Accreditation Manual

Foundation for the Accreditation of Cellular Therapy

JACIE joint accreditation committee isct ebmt

THIRD EDITION, 2007

CELLULAR THERAPY PRODUCT COLLECTION, PROCESSING, AND ADMINISTRATION
ACCREDITATION MANUAL

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

Third Edition
November 2007

NOTICE

FACT-JACIE Standards are designed to provide minimum guidelines for facilities and individuals performing hematopoietic cell transplantation and therapy or providing support services for such procedures. These Standards are not intended to include all procedures and practices that a facility or individual should implement if the standard of practice in the community or governmental laws or regulations establish additional requirements. Each facility and individual should analyze its practices and procedures to determine whether additional standards apply. The Foundation for the Accreditation of Cellular Therapy and the Joint Accreditation Committee – ISCT and EBMT disclaim any responsibility for setting maximum standards and expressly do not represent or warrant that compliance with the Standards is an exclusive means of complying with the standard of care in the industry or community.

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FACT-JACIE Accreditation Manual

INTRODUCTION

This manual is intended to accompany the FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing and Administration, Third Edition, 2006. The purpose of the Accreditation 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, and are beyond the scope of this Manual. 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. It is not an exhaustive list of possible ways to meet the Standards, but to provide examples only since there are many effective mechanisms by which to achieve compliance with FACT-JACIE Standards.

This guidance manual is organized by the alphanumeric order of the Standards. Each Standard is quoted in its entirety, followed by the Accreditation Checklist questions pertaining to that Standard. The Standards are followed by the guidance section, which includes explanations, examples and additional educational references. The clinical and processing facility portions of the manual, Sections B and D, are self-explanatory.

The major objective of the *FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing and Administration* 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. *FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing and Administration* apply to all phases of collection, processing, storage, and administration of these cells that have been derived from marrow or peripheral blood, 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, applying the clinical standards for transplantation of allogeneic or autologous hematopoietic progenitor cells, 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, Processing, Testing, Banking, Selection and Release*.

FACT-JACIE Standards are designed to provide minimal performance guidelines for facilities and individuals performing hematopoietic cell transplantation and therapy or providing support services for such procedures. FACT-JACIE Standards are not intended to include all procedures and practices that a facility or individual should implement if the standard of practice in the community or federal or state laws or regulations establish additional requirements. Each facility and individual should analyze their practices or procedures to determine whether additional standards apply. FACT-JACIE disclaims any responsibility for setting maximum standards and expressly does not represent or warrant that compliance with the Standards is an exclusive means of complying with the standard of care in the industry or community.

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. Every attempt has been made in this companion manual to use these two words in the same way as they are used in Standards. Wherever there is a discrepancy, the term used in the Standards shall prevail.

ABBREVIATIONS

The following abbreviations cover terms used in these Standards:

ABO	Major human blood group including erythrocyte antigens, A, B, O
AC	Accompany
AF	Affixed
Anti-	Antibody to the antigen designated
ASHI	American Society for Histocompatibility and Immunogenetics
AT	Attached
CFR	Code of Federal Regulations
CIBMTR	Center for International Blood and Marrow Transplant Research
CMS	Centers for Medicare and Medicaid Services
CLIA	Clinical Laboratory Improvement Amendments
CMV	Cytomegalovirus
DNA	Deoxyribonucleic acid
EBMT	European Group for Blood and Marrow Transplantation
EFI	European Federation for Immunogenetics
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	U. S. Food and Drug Administration
HLA	Human Leukocyte Antigen
HPC	Hematopoietic progenitor cells
IDE	Investigational device exemption
IND	Investigational new drug
ISCT	International Society for Cellular Therapy
JACIE	Joint Accreditation Committee – ISCT and EBMT
PBSC	*Peripheral Blood Stem Cells*
RBC	Red blood cell
Rh	Rhesus systems of human red cell antigens; used in this document to refer to the Rh(D) antigen only, unless otherwise specified
USDA	United States Department of Agriculture

DEFINITIONS

Accompany: To go or be together with, but not attached. Information that must accompany a cellular therapy product in a sealed package, or alternatively, be attached or affixed.

Accreditation Cycle: The period of time from the awarding of accreditation until its expiration. At publication of these Standards, this period is three (3) years.

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 to the collection or infusion of any cellular therapy product for which there is a reasonable possibility that the cellular therapy product caused the response.

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

Allogeneic: Cellular therapy product obtained from a donor and intended for infusion into a genetically distinct recipient.

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 products, reagents, specimens, patients, 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 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: Cellular therapy product obtained from a donor and intended for infusion back into the same individual.

Available for distribution: The point at which the cellular therapy product has been determined to meet all release criteria.

Biological product deviation: A deviation from applicable regulations, standards, or established specifications that relate to the prevention of communicable disease transmission or cellular therapy product contamination; or an unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease or may lead to cellular therapy product contamination.

Calibrate: To set measurement equipment against a known standard.

Calibration: Periodic scheduled activity to check and maintain the accuracy of measurements 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, pancreatic islets) that is procured from a donor and intended for processing and administration.

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 hematopoietic 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 in the same metropolitan area shall demonstrate evidence of regular interaction and common protocols, staff training procedures, quality management systems, and review of clinical results. Several clinical sites, particularly with different Directors, or outside a single metropolitan area, joining together for the purpose of meeting criteria to qualify as a Clinical Program do not fulfill the intent of these Standards. In contrast, collection facilities and/or processing facilities serving one or more clinical programs are acceptable.

Collection: Any procedure for harvesting cellular therapy products, including labeling, regardless of technique or source.

Collection Facility: The site where a cellular therapy product is collected from a donor.

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 distributed cellular therapy product or with a service related to the collection, processing, storage, distribution, or infusion 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.

Current Good Tissue Practice: The methods used in, and the facilities and controls used for, the manufacture of HCT/Ps including recordkeeping and the establishment of a quality program as required by the FDA for HCT/P establishments.

Designee: An individual with appropriate experience or expertise who is given the authority to assume a specific responsibility.

Director: For purposes of these Standards, includes individuals with the following qualifications:

> *Clinical Program Director* is the physician responsible for all administrative and clinical operations of the clinical transplantation program, including compliance with these Standards. The Clinical Program Director shall be appropriately licensed to practice medicine in the jurisdiction in which the program is located and board certified (or non-U.S. equivalent) in one or more of the following specialties: Hematology, Medical Oncology, Adult or Pediatric Immunology, or Pediatric Hematology/Oncology. A non-board certified physician who completed medical training prior to 1985 may serve as Clinical Program Director if she/he has documented experience and published contributions in the field of hematopoietic cell transplantation extending over ten years. The Clinical Program Director shall participate regularly in educational activities related to the field of hematopoietic cell transplantation. The Clinical Program Director also has oversight of the care provided by the Clinical Program.

Collection Facility Director is an individual with a medical degree or doctoral degree in a relevant science, qualified by postgraduate training or experience for the scope of activities carried out in the Collection Facility. The Collection Facility Director is responsible for all technical procedures, performance of the collection procedure, supervision of staff, and administrative operations of the Collection Facility. The Collection Facility Director shall participate regularly in educational activities related to the field of cellular therapy product collection and/or transplantation. The Collection Facility Director may also serve as the Medical Director if appropriately credentialed.

Collection Facility Medical Director is a licensed physician with postgraduate training in cell collection and/or transplantation. This individual, or designee, is directly responsible for the medical care of patients undergoing apheresis or marrow harvest, including the pre-collection evaluation of the donor at the time of donation and care of any complications resulting from the collection procedure. The Collection Facility Medical Director shall participate regularly in educational activities related to the field of cellular therapy product collection and/or transplantation. The Collection Facility Medical Director may also serve as the Collection Facility Director if appropriately credentialed.

Processing Facility Director is an individual with a medical degree or a 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 is responsible for all procedures and administrative operations of the Processing Facility, including compliance with these Standards. The Processing Facility Director shall participate regularly in educational activities related to the field of cellular therapy processing and/or transplantation. The Processing Facility Director may also serve as the Processing Facility Medical Director if appropriately credentialed.

Processing Facility Medical Director is a licensed physician with postgraduate training and/or one year experience in the preparation and clinical use of cell therapy products. The Processing Facility Medical Director or designee is directly responsible for all medical aspects related to the Processing Facility. The Processing Facility Medical Director shall participate regularly in educational activities related to the field of cellular therapy product processing and/or transplantation. The Medical Director may also serve as the Processing Facility Laboratory Director if appropriately credentialed.

Distribution: Any conveyance or shipment (including importation and exportation) of a cellular therapy product that has been determined to meet appropriate release criteria, whether or not such conveyance or shipment is entirely intrastate.

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

Electronic record: Any 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: A cellular therapy product donor who meets all donor screening and testing requirements related to transmission of infectious disease as defined by the FDA or non-U.S. equivalent.

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 or electronically, implement, follow, review, and, as needed, revise on an ongoing basis.

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

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.

Gene insertion: The introduction of one or more exogenous genes into one or more cell populations.

Hematopoietic progenitor cells (HPC): 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 cell 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: A cellular therapy product donor who does not meet all donor screening and testing requirements related to transmission of infectious disease as defined by the FDA, or non-U.S. equivalent.

Institutional Review Board or Ethics Committee: A Board or Committee established by an institution in accordance with the regulations of the U.S. Department of Health and Human Services, or other governmental agency where applicable, to review biomedical and behavioral research involving human subjects conducted at or supported by that institution.

ISBT 128: The international information technology standard for transfusion medicine and transplantation.

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.

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 the time of collection and not subjected to any form of manipulation.

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.

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 depleted.

Nurse Practitioner: A nurse with a graduate degree in advanced practice nursing providing patient services in defined areas of practice in collaboration with other health professionals.

New Patient: For purposes of these Standards, a New Patient refers to an individual undergoing the specified type (autologous, syngeneic, or allogeneic) of transplantation for the first time in the Clinical Program whether or not that patient was previously treated by that Clinical Program.

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.

Physician Assistant: A person formally trained to provide diagnostic, therapeutic, and preventive health care services with physician supervision.

Policies: Documents that define the scope of an organization, explain how the goals of the organization will be achieved, and/or serve 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 of a potential discrepancy or other undesirable situation to prevent such an occurrence.

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 infusion 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 quantity of product removed from the cellular therapy product.

*Products**:

The proper name of each product is as follows:

HPC, Apheresis: Hematopoietic Progenitor Cells obtained from a mobilized donor by an automated apheresis procedure.

HPC, Cord Blood: Hematopoietic Progenitor Cells obtained from umbilical cord and/or placental blood at the time of delivery.

HPC, Marrow: Hematopoietic Progenitor Cells aspirated from the iliac crests, sternum, or other bones of an autologous or allogeneic donor.

HPC, Whole Blood: Whole Blood collected for HPC contained within it.

TC, Apheresis: Nucleated cells obtained by an apheresis procedure intended for therapeutic use other than as HPC.

TC, Cord Blood: Nucleated cells collected from umbilical cord and/or placental blood intended for therapeutic use other than as HPC.

TC, Marrow: Nucleated cells collected from bone marrow intended for therapeutic use other than as HPC.

TC, Whole Blood: Nucleated cells collected from whole blood intended for therapeutic use other than as HPC.

TC-T Cells: A therapeutic cell product from any source containing a quantified T lymphocyte population.

TC-Cytotoxic Lymphocytes: A therapeutic cell product containing an enriched preparation of Cytotoxic Lymphocytes.

TC-T Reg Cells: A therapeutic cell product containing an enriched population of regulatory T lymphocytes.

TC-DC: A therapeutic cell product containing dendritic cells prepared for therapeutic use.

TC-NK Cells: A therapeutic cell product containing an enriched preparation of Natural Killer Cells.

TC-Tumor Derived: A product containing malignant cells or elements derived from them.

TC-MSC: A therapeutic product containing mesenchymal stromal cells isolated by suitable technologies, expanded, and processed for therapeutic use.

**ISBT 128* official product nomenclature will be adopted when finalized.

*Product modifications**:

B-Cell Reduced: Cells processed by negative selection for B lymphocytes.

Buffy Coat Enriched: Cells remaining after removal of a portion of the mature erythrocytes and plasma by centrifugation and/or sedimentation using devices, supplies, and techniques validated for the procedure(s).

CD34-Enriched: Cells processed by positive selection for CD34-antigen bearing cells.

Cryopreserved: Cells frozen using devices, supplies, and techniques validated to maintain viability.

Density Enriched: Cells remaining after depletion of mature erythrocytes, polymorphonuclear leukocytes, and plasma by techniques using defined density gradient medium and devices and reagents validated for the separation of cells based on density.

Ex Vivo Expanded: Cells that have been cultured in vitro for the purpose of producing and/or enriching for a specific functional subset.

Gene-Manipulated: Cells that have been processed to alter their own genes or introduce new genetic material.

Plasma and RBC Reduced: Cells remaining after removal of a portion of the mature erythrocytes and plasma by sedimentation and/or centrifugation, using devices, supplies, and techniques validated for the process.

Plasma Reduced: Cells remaining after removal of a portion of the plasma by sedimentation and/or centrifugation using devices, supplies, and techniques validated for the procedure(s).

RBC Reduced: Cells remaining after removal of a portion of the mature erythrocytes by sedimentation, centrifugation, or lysis using devices, supplies, and techniques validated for the procedure(s).

T-Cell Depleted: Cells processed by negative selection for T lymphocytes.

Tumor Cell Depleted: Cells processed by negative selection for tumor cells.

**ISBT 128* official product nomenclature will be adopted when finalized.

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

Protocol: A written document describing steps of a treatment or experimental 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 processes, equipment, 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 activities. The purpose of a quality audit is to verify, by examination and evaluation of objective evidence, the degree of compliance with those aspects of the quality program under review.

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

Quality improvement: The actions, planned and performed, to develop a system to review and 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.

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.

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.

Release: Removal of a product from quarantine or in-process status for distribution.

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.

Standard Operating Procedures Manual: A compilation of written detailed instructions required to perform procedures.

Standards: The current edition of the *International Standards for Cellular Therapy Product Collection, Processing, and Administration* published by FACT-JACIE.

Storage: Holding a cellular therapy product for future processing and/or distribution.

Syngeneic: Cellular therapy product collected from a donor and intended for infusion into a genetically identical twin.

Therapeutic cells (TC): 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 autologous, syngeneic, or allogeneic HPC with the intent of providing transient or permanent engraftment in support of therapy of disease.

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.

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

FACT-JACIE ACCREDITATION PROCESS

Facilities performing hematopoietic progenitor cell collection, processing, storage, and/or transplantation may apply for voluntary accreditation by FACT in North America or Australia, or by JACIE in Europe as described below. Applicants from other areas are encouraged to contact FACT for direction in applying for accreditation.

1) A clinical hematopoietic progenitor cell transplantation program may apply for accreditation alone or in conjunction with the collection facility and/or the cell processing facility with which it is associated. All facilities applying together should submit pre-inspection data together. If applying separately, a clinical transplant program must use a collection facility and a processing laboratory that meet FACT-JACIE Standards and have a clearly defined contractual or reporting relationship.

2) A hematopoietic progenitor cell collection facility or service (peripheral blood or bone marrow) may apply for accreditation as an integral part of a clinical transplant program, as a local or regional collection service providing hematopoietic progenitor cell collection services for one or more clinical transplant programs, or in conjunction with a cell processing facility if the services of hematopoietic progenitor cell collection and processing/storage are functionally linked. An accredited hematopoietic progenitor cell collection facility may provide services for clinical transplant programs that are or are not FACT or JACIE accredited, but shall use a processing facility that meets FACT-JACIE Standards.

3) A hematopoietic progenitor cell processing facility may apply for accreditation as an integral part of a clinical transplant program, as part of a collection service or facility, or as an independent laboratory that processes and stores hematopoietic progenitor cell products for clinical program(s) or collection facilities. An accredited processing facility may provide services for clinical transplant programs and/or collection services that are or are not FACT or JACIE accredited.

Accreditation of the clinical hematopoietic progenitor cell transplantation program may be for allogeneic transplantation, autologous transplantation, or both. In addition, a program may be accredited as a combined pediatric and adult medicine program if criteria are met. The accreditation covers cellular therapy products derived from bone marrow and/or peripheral blood. Accredited facilities will be reinspected every three years or in response to complaints or information that a facility may be non-compliant with the Standards, or as determined by the FACT or JACIE Board of Directors. Accreditation may be suspended or terminated if a program or facility fails to comply with the Standards.

The basis for FACT or JACIE Accreditation is documented compliance with the current edition of these Standards. Although there are joint FACT-JACIE Standards, FACT and JACIE maintain separate and parallel accreditation processes. Accreditation is determined by evaluation of written information provided by the applicant facility and by on-site inspection. All inspections are conducted by persons qualified by training and experience in hematopoietic cell therapy, who are affiliated with an accredited or applicant facility, have attended inspector training and at least one inspection as a trainee, and who have a working knowledge of FACT-JACIE Standards and of their application to various aspects of hematopoietic progenitor cell therapy. For each inspection, inspectors are chosen to ensure that the team has the depth and breadth of expertise and experience to adequately survey the applicant program. Applicants are entitled to request a change of inspectors prior to the inspection if there is any perceived conflict of interest. The on-site inspection is based on a checklist methodology, in which the applicant first answers each question, and these answers are verified by the on-site inspectors. This methodology is effective in focusing the content of the inspection on the FACT-JACIE Standards, and in promoting thoroughness and consistency among inspectors and inspections. The completed checklists,

labels, and other submitted documents, and the inspectors' final report serve as the basis for review by the FACT or JACIE Accreditation Committee and Board of Directors, as appropriate. Following the on-site inspection and review, facilities and programs found to be out of compliance with some Standards are given time to correct the noted deficiencies. The goal is to raise the quality bar in all programs and assist practitioners in achieving accreditation. Depending on the number and severity of the deficiencies noted, a focused on-site reinspection may or may not be necessary. Accreditation is valid for three years. FACT or JACIE accredited programs are published on their respective web sites. Accredited programs are required to document their continued compliance with Standards by submission of annual program information. Any program or facility that has been denied accreditation during this process is entitled to appeal that decision by written explanation.

For additional information regarding accreditation or any of the policies and procedures of FACT, the reader is referred to the FACT National Office in Omaha, Nebraska or to the FACT web site at: *www.factwebsite.org*.

For information related to the JACIE accreditation process, please visit the web site at: *www.jacie.org*.

ACCREDITATION MANUAL – SECTION B
CLINICAL PROGRAM STANDARDS

B1 GENERAL

STANDARD:

B1.1 The Clinical Transplantation Program "Clinical Program" consists of 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 hematopoietic 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 in the same metropolitan area shall demonstrate common protocols, staff training procedures, quality management systems, and review of clinical results and evidence of regular interaction. Several clinical sites, particularly with different Directors, or outside a single metropolitan area, joining together for the purpose of meeting criteria to qualify as a Clinical Program do not fulfill the intent of these Standards.

GUIDANCE:

This standard is the definition of a Clinical Program, an entity that can be inspected and accredited. The questions on the inspection application and checklist are designed to elicit the information necessary to determine if a single transplant program exists. In some cases, some but not necessarily all of the components of a single program may be present. The Accreditation Committee will individually evaluate each of these situations after the report of the inspection team has been submitted. A Clinical Program may have one or more transplant sites.

Programs that include non-contiguous sites must be sites within the same metropolitan area. In the US this is defined as a metropolitan statistical area (MSA). The definition of a US metropolitan statistical area is taken from the U.S. Office of Management and Budget (OMB) and published by the Bureau of the Census in the Statistical Abstract of the United States, 1995, which states that "The general concept of an MA (Metropolitan Area) is that of a core area containing a large population nucleus, together with adjacent communities having a high degree of economic and social integration with that core. Currently defined MSAs are based on application of 1990 standards (which appeared in the Federal Register on March 30, 1990) to 1990 decennial census data."

The current standards provide that each MSA must include at least: (a) One city with 50,000 or more inhabitants, or (b) A Census Bureau-defined urbanized area of at least 50,000 inhabitants and a total metropolitan population of at least 100,000 (75,000 in New England). Adjacent counties are included in a metropolitan statistical area if at least 50% of the population resides in the urbanized area; outlying counties are also included if they meet specified requirements of commuting to the central counties and other selected requirements of metropolitan character such as population density and percent urban. As of the June 1993 OMB announcement, there were 268 MSAs in the United States. This list will be used as the basis for interpretation of this standard. Non-contiguous sites outside of a single metropolitan statistical area will not be considered to be a single program. For JACIE purposes, this standard will be interpreted as meaning that the different clinical units that make up a single program be close enough to allow for close and regular interaction. As an indicator, units should be no more than 1 hour travelling distance in each direction.

It is possible to have one or more than one Clinical Program in a metropolitan area. Each could be separately accredited if each alone meets the criteria detailed in the Standards document. 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 should apply as one program.

This standard means that clinicians accredited together as a program must work together in readily demonstrable ways on a daily basis, and have a single leader (the Program Director) or Co-Directors, each of whom is responsible for these clinical transplant activities. In evaluating whether several noncontiguous sites constitute a program, the inspector will expect to find some of the following if a single program exists:

1) Common or equivalent staff training programs, especially for nurses. This would include in-service training and competency testing in the same topics.

2) 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.

3) 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, laboratory meetings, etc.

4) Regular interaction should involve physicians, nurses, coordinators, social workers, education consultants, laboratory 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.

5) A common database of all patients treated by the program, including a single statistical support group and/or data managers.

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 transplant programs. For example, a hematopoietic progenitor cell (HPC) collection facility may be accredited independently, or in conjunction with a Clinical Program and/or with a cell processing laboratory. A Clinical Program and the collection facility could be joint facilities, with the cells processed and stored at a distant site. A cell processing laboratory may process and store cells for several 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.

STANDARD:

B1.1.1 A Clinical Program may have more than one clinical site in different hospitals if the other criteria in B1.1 are met.

GUIDANCE:

A program may undertake transplants at more than one site. In most cases each site would be located at a discrete hospital. For example, a program may have an adult unit at an adult hospital and a pediatric unit at a children's hospital or one 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 abide by all applicable governmental laws and regulations.

B1.3 If the Clinical Program requests accreditation for allogeneic transplantation, a minimum of ten (10) new allogeneic patients shall have been transplanted during the twelve month period immediately preceding the application for program accreditation and annually thereafter. A Clinical Program that is accredited for allogeneic transplantation will be considered to have met the numeric requirement for autologous transplantation.

B1.3.1 For Clinical Programs utilizing more than one clinical site and requesting accreditation for allogeneic transplant, a minimum of five (5) new allogeneic patients shall have been transplanted at each site during the twelve month period immediately preceding the application and annually thereafter. A site that is accredited for allogeneic transplantation will be considered to have met the numeric requirement for autologous transplantation.

B1.3.2 For a combined Clinical Program caring for pediatric and adult patients on the same site, Clinical Programs shall perform five (5) allogeneic transplants for each population.

GUIDANCE:

To ensure continuing proficiency in a transplant program, a minimum volume of patients must be treated in the 12-month period preceding submission of the application, and annually thereafter. Note in this standard, the 10 per year for the 12 months prior to application for accreditation is "shall" (required). If the program is requesting accreditation for allogeneic or allogeneic and autologous transplant, at least 10 new allogeneic patients should have been transplanted. There is no minimum requirement for autologous transplant for centers performing allogeneic transplants, as it was felt that proficiency in allogeneic transplant is a sufficient criterion for performing autologous transplant.

For combined Adult and Pediatric Programs or programs 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. Programs that do not meet the minimum patient volumes may be placed on "probation." The program will be required to submit a plan to ensure minimum patient volumes, and may have accreditation removed if these requirements are not met.

For a combined Adult and Pediatric 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.

The term “new allogeneic patient” or “new autologous patient” refers to a patient who will be receiving their first transplant of each type. Patients receiving second or subsequent transplants of the same type, regardless of the time interval between transplants, will not be counted towards a program’s volume. For example:

1) A patient receiving tandem autologous transplants would count as one new autologous patient.

2) A patient who received an autologous transplant and subsequently received an allogeneic transplant would count as one new autologous and one new allogeneic patient.

3) A patient who received an allogeneic transplant, then relapsed and received a second allogeneic transplant from a different donor would count as one new allogeneic patient.

Because of the mix of patients and transplant types in a particular transplant center, 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.

STANDARD:

B1.4 If the Clinical Program requests accreditation for only autologous transplant, a minimum of five (5) new recipients of autologous transplant shall have been transplanted during the twelve month period immediately preceding the application for accreditation and annually thereafter at each site.

GUIDANCE:

If the program is requesting accreditation for autologous transplant only, at least five new autologous patients must have been transplanted in the 12 months prior to submission of a new application, and each year of the three-year cycle for renewal applications. Five autologous patients at each site and for each population (adult, pediatric) transplanted are required in the 12 months preceding application (and yearly thereafter). A center performing autologous transplants alone would not be eligible for accreditation for allogeneic transplants until they met the annual requirement of 10 new allogeneic patients because of the specific competencies required for care of allogeneic transplant patients.

The term "new allogeneic patient" or "new autologous patient" refers to a patient who will be receiving their first transplant of each type. Patients receiving second or subsequent transplants of the same type, regardless of the time interval between transplants, will not be counted towards a program's volume (see above).

B2 CLINICAL UNIT

STANDARD:

B2.1 There shall be a designated inpatient unit that minimizes airborne microbial contamination.

B2.2 The Clinical Program's inpatient unit shall be located in a facility accredited by the Joint Commission on Accreditation of Healthcare Organizations or equivalent, if applicable.

B2.3 There shall be a designated area for outpatient care that reasonably protects the patient from transmission of infectious agents and allows, as necessary, for appropriate patient isolation, and administration of intravenous fluids, medications, and/or blood products.

GUIDANCE:

The inspector will want to tour the inpatient unit during the on-site inspection. The type of air handling should be documentable from a facilities management office. The inspector should observe if the signs posted around the unit and the behavior of the staff during the visit are consistent with what would be expected for the type of air handling/isolation that is said to be in place. It should be observed if there are single rooms, closed doors, hand-washing facilities, etc.

The manner in which various units meet this requirement may vary depending on the type of patient being treated (i.e., mismatched or T-cell depleted, unrelated allogeneic recipient, autologous Peripheral Blood Stem Cells [PBSC] recipient). The standard is not meant to imply that every unit must have laminar airflow available. HEPA filtration with positive pressure is recommended for high-risk patients, but is not required for every unit. Rooms should normally be sited on a single unit where infection control policies can be implemented. Care should be taken to ensure that the ventilation from other isolation rooms (where infected patients may reside) does not pass through the rooms used for HPC patients.

This standard is also 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.

An ambulatory unit that provides space for outpatient visits, infusions, and transfusions may comply with this standard. The Program should provide a plan for the outpatient unit to provide, as necessary, provisions for isolation of patients, administration of fluids and blood products. 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.

It is acceptable to use a portion of an inpatient unit for outpatient visits.

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.

GUIDANCE:

The Emergency Room may be acceptable when other outpatient facilities are unavailable, if the physician coverage is adequate to ensure that the HPC recipients are evaluated promptly (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 an adequate number of nurses experienced in the care of transplant patients.

B2.4.3 There shall be a nurse/patient ratio satisfactory to cover the severity of the patients' clinical status.

GUIDANCE:

The intent of this standard is to acknowledge that nursing needs of patients vary. 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, a smaller number of staff should be able to care for the patients. Thus, there is no magic number or ratio sought, but some demonstration that sufficient flexibility exists within the pool of trained staff to meet the intensive patient needs when they occur. The inspector may ask to meet with the Head Nurse for the Program to assess how the nursing staffing issues are handled.

STANDARD:

B2.4.4 There shall be a pharmacy providing 24-hour availability of medications needed for the care of transplant patients.

GUIDANCE:

In addition to having medications available, the Pharmacy should have mechanisms to prevent dosing errors in the administration of high-dose therapies. A written protocol for dose verification by the Pharmacy staff could provide documentation of compliance.

STANDARD:

B2.4.5 There shall be the ability to perform dialysis under the direction of Nephrologists and trained personnel.

GUIDANCE:

The Program should have documentation that there is ready access for its patients to be dialyzed if the need arises. This can 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.

STANDARD:

B2.4.6 There shall be a transfusion service providing 24-hour availability of CMV appropriate and irradiated blood products needed for the care of transplant patients.

GUIDANCE:

Those blood components suitable for CMV-negative recipients must be defined in the Standard Operating Procedures (SOPs) by the Clinical Program. If leukocyte-reduction is used to meet this standard, there must be a validated method in place (in the Transfusion Service) to ensure that components are suitably leukocyte-reduced. There shall be a procedure in place for procurement of irradiated blood products as needed for patient care.

STANDARD:

B2.4.7 There shall be immediate access to an intensive care unit or equivalent coverage for critically ill patients.

GUIDANCE:

The Program should 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.

STANDARD:

B2.4.8 Clinical Programs performing allogeneic hematopoietic cell transplants shall use HLA testing laboratories 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.

GUIDANCE:

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 stringent requirements. Documentation required is a copy of the current (in-date) ASHI, EFI, or equivalent accreditation certificate for the laboratory to include at least the above listed competencies.

STANDARD:

B2.5 SAFETY REQUIREMENTS

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

B2.5.2 The Clinical Program shall include instructions for action in case of exposure to communicable disease or to chemical, biologic, or radiological hazards in its safety manual.

B2.5.3 The Clinical Program shall dispose of medical waste in a manner that minimizes any hazard to facility personnel and to the environment in accordance with applicable governmental laws and regulations.

B2.5.4 The Clinical Program shall ensure that the Clinical Units are operated in a clean, sanitary, and orderly manner.

B2.5.5 Gloves shall be worn while handling biological specimens.

GUIDANCE:
This standard applies to all facilities involved in hematopoietic progenitor cell therapy (Clinical Programs, Collection, and Processing Facilities). Safety training, including universal precautions ("standard" precautions per the Centers for Disease Control) for handling blood is a requirement of the Occupational Safety and Health Administration in the US. Equivalent regulations apply in other countries. The facility's policies and procedures, including housekeeping and waste disposal, must document consistency with good biosafety procedures, including adherence to universal precautions and to federal, state, or provincial regulations regarding safety.

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 hematopoietic progenitor cell 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. There must clearly be demonstrated policies and procedures for both a general chemical safety plan as well as a safety plan for spillage or contamination of areas from chemotherapy.

Any potentially biohazardous material shall be discarded in a safe manner according to written protocols for the disposal of biohazard waste. Contaminated materials may be discarded by autoclaving, ultra-high temperature incineration, decontamination with hypochlorite solution, and, in some locations, the use of a landfill. Radioactive waste must be discarded using methods approved by appropriate governmental agencies. Also, facilities should post warning signs wherever radioactive materials are in use. Facility personnel responsible for these activities should be identified.

Each facility shall have a safety manual. 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. The facility may keep a condensed or summarized hard copy of the institutional safety manual in the Clinical Facility. In this case, there must be written documentation of how the safety manual is kept updated with institutional revisions. Alternatively, an SOP that defines the location of hard copies of the institutional safety manual, in the event of computer failure, will suffice. 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. Safety, infection control or biohazard waste disposal procedures that are unique to the Clinical Facility should be covered in the Clinical Facility SOP manual.

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. The inspector should examine employee files for compliance and training in biological, chemical, and radiation safety (when appropriate) in addition to reviewing safety procedures. The inspector should examine how products are being handled and discarded (e.g., incinerator, waste field, etc.) and compare his/her observations with the written

protocols. Compliance with state, national, and international 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.

B3 PERSONNEL

STANDARD:

B3.1 CLINICAL TRANSPLANT TEAM

B3.1.1 A dedicated transplant team including a Clinical Program Director and at least one other physician trained and/or experienced in cell therapy shall have been in place for at least twelve (12) months prior to being eligible for initial accreditation.

GUIDANCE:

The standard requires that a transplant 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 transplant program, that new program must have been in place a year and the team must perform a minimum number of transplants (per B1.3 and B1.4) prior to application for 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-JACIE policies. Changes in a Clinical Program Director, Laboratory Director, or Collection Facility 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 program is relatively small and physicians relocate, reinspection may be required when new physicians are appointed. Likewise, if the entire Collection or Laboratory Facility personnel left the 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). It is the responsibility of the Clinical 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 the Annual Reporting Form sent to all accredited facilities on the anniversary of their accreditation date.

STANDARD:

B3.1.2 Clinical Programs performing pediatric transplantation shall have a transplant team trained in the management of pediatric patients.

B3.1.3 Clinical Programs performing pediatric transplantation shall have at least one attending physician who is board certified/eligible (or non-U.S. equivalent) in Pediatric Hematology/Oncology or Pediatric Immunology.

B3.1.4 For Clinical Programs performing adult transplantation, there shall be at least one attending physician who is board certified/eligible (or non-U.S. equivalent) in Hematology, Medical Oncology, or Immunology.

GUIDANCE:
There is no separate accreditation for pediatric and adult transplant programs. The standards do require, however, 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. Evidence of compliance with these standards may include age-specific competencies and proficiencies, attendance of age-specific continuing educational activities and age-specific preceptorships. Teams treating children must include an attending physician who is board certified or eligible in Pediatric Hematology/Oncology or Pediatric Immunology or non-U.S. equivalent. Teams treating adults must include an attending physician who is board certified/eligible in Hematology, Medical Oncology or Immunology, or non-U.S. equivalent. 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.

STANDARD:

B3.1.5 The Clinical Program shall have access to licensed physicians who are trained and competent in bone marrow harvesting and a bone marrow collection facility that meets FACT-JACIE Standards.

B3.1.6 The Clinical Program shall have access to personnel who are trained and competent in cellular product collection by apheresis and an apheresis facility that meets FACT-JACIE Standards.

GUIDANCE:
This standard requires that the program have access to at least one physician who is trained and competent in bone marrow harvesting. Centers that never harvest bone marrow for use in treatment of their transplant patients are exempt from this requirement but must document a contingency plan if mobilization fails or a sufficient volume cannot be collected. Evidence of training may include documentation by a letter of 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.

Bone marrow harvesting must be performed in a facility that meets FACT-JACIE Standards. The increased use of peripheral blood as a source of hematopoietic progenitors 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 Bone Marrow Collection Facility is one procedure in the 12 months prior to initial application for accreditation or three procedures in a three year re-accreditation cycle, as defined in C1.3.2 and C1.5. Centers harvesting bone marrow must document compliance with all requirements of section C of these Standards.

STANDARD:

B3.2 CLINICAL PROGRAM DIRECTOR

B3.2.1 The Clinical Program Director shall be appropriately licensed to practice medicine in the jurisdiction in which the program is located and board certified (or non-U.S. equivalent) in one or more of the following specialties: Hematology, Medical Oncology, Adult or Pediatric Immunology, or Pediatric Hematology/Oncology. Non-board certified physicians who completed medical training prior to 1985 may serve as Clinical Program Director if they have documented experience and published contributions in the field of hematopoietic cell transplantation extending over ten (10) years.

GUIDANCE:
The Program Director must be licensed to practice medicine in the country where the program is located. Appropriately licensed means that the Program Director must be licensed to practice medicine in the state, province, or country where the transplant program is located. To fulfill this standard, the Program Director must provide a copy of his or her current medical license. Since documentation of the M.D. degree is required to obtain a medical license, the license will be considered documentation that the Program Director is a physician.

The Program Director must be currently board-certified (or non-U.S. equivalent) in one or more of the specialties listed. When board certification is required, the certification must be kept current. Board-eligible is not considered adequate for the Director. Required documentation is a photocopy of the current certificate from the relevant Board, or equivalent documentation in non-U.S. countries. Immunology is considered to be a relevant discipline because of its pivotal role in the science of transplantation and because of the immunological disorders that may be cured by transplantation. It may also be critical in the therapy of cancer, where transplantation is used to treat large numbers of patients. Individuals with board certification, or non-U.S. equivalent 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.

The European equivalent requirements include specialist registration or completion of the higher specialist training in one of the specialties listed in B3.2.1. Where physicians received training outside Europe or the U.S., the JACIE Accreditation Committee will access their documentation of training and the JACIE Board will make the final determination.

Those physicians who received all or part of their medical and specialty training outside of the United States may be ineligible to become Board-certified in the U.S. on this basis alone. These physicians 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 American Board certification. The FACT Board of Directors will make the final determination.

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 board exams. Those physicians who completed their medical training prior to the availability of specific training in transplantation (i.e., prior to 1985) may be qualified as Program Directors if they have at least 10 years of documented experience in transplantation and published contributions in the field of hematopoietic progenitor cell transplantation. The 10 years experience must be documented in the form of a work history, including the size and complexity (i.e., autologous transplant only, autologous and allogeneic, unrelated donors, allogeneic with T-Cell depletion, etc.) of the programs in which the applicant Program Director has worked 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. In addition, there must be 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.

STANDARD:

B3.2.2 The Clinical Program Director shall have at least one year of specific clinical training in HPC transplantation as defined in B3.4, <u>or</u> two (2) years experience as an attending physician responsible for the clinical management of HPC transplant patients in the

inpatient and outpatient settings. The Clinical Program Director shall have written confirmation of his/her training or experience from the Director of the Clinical Program, department, or institution in which that training or experience was obtained.

B3.2.3 The Clinical Program Director shall be responsible for administrative and clinical operations, including compliance with these Standards.

B3.2.4 The Clinical Program Director shall have oversight of 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.

GUIDANCE:
This standard is not intended to preclude the prerogative of the Program Director to delegate some of the duties associated with the operation of the Program to other qualified individuals. For example, individual attending physicians (or non-U.S. equivalent) may accept patients or donors for entry into the program according to institutional standards, but it is the responsibility of the program director (or his/her designee) to ensure review and compliance with those standards. 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 program elements, internal or contracted, will fall to the 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 QM plan.

STANDARD:

B3.2.5 The Clinical Program Director shall have oversight of the medical care provided by the Clinical Program including medical care provided by the physicians on the transplant team. The Clinical Program Director is responsible for verifying the knowledge and skills of the physicians of the transplant team. Management of the Clinical Unit may be delegated to a Medical Director who fulfills the requirements in B3.3.

GUIDANCE:
This standard is not meant to imply that the Program Director is directly responsible for the medical activity of another physician. The Program Director is responsible to review the knowledge and skills of the transplant physicians as well as the medical care provided. This review must be documented by some means, such as evidence of Continuing Medical Education (CME), annual faculty evaluations (in the case of academic programs), merit raises, minutes of meetings in which the medical care of patients was specifically addressed, etc. The Program Director may delegate the management of the Clinical Unit as well as the oversight of physician knowledge, skills, and medical care to a qualified physician.

STANDARD:

B3.2.6 The Clinical Program Director shall participate regularly in educational activities related to the field of HPC transplantation.

GUIDANCE
The field of transplant medicine continues to evolve rapidly. Program directors should participate regularly in educational activities related to the field. Evidence of compliance may include either formal or informal study, such as meets the requirements of AMA type I or II or applicable national continuing education programs. Presentation of CME lectures, papers at scientific meetings, or publication of manuscripts related to transplantation may also meet this standard.

STANDARD:

B3.3 ATTENDING PHYSICIANS

B3.3.1 Clinical Program attending physicians shall be appropriately licensed to practice medicine in the jurisdiction of the Clinical Program and should be board certified or eligible (or non-U.S. equivalent) in one of the specialties listed in B3.2.1.

B3.3.2 Clinical Program attending physicians shall have specific clinical training in HPC transplant medicine as defined in B3.4.

B3.3.3 Clinical Program attending physicians shall participate regularly in educational activities related to the field of HPC transplantation.

GUIDANCE:

This standard is parallel to the requirements for the Program Director, however, it allows for board-eligible for attending, or non-U.S. equivalent, physicians. In Europe, this includes consultant/senior physicians who have completed higher specialist training but are not on the higher specialist register.

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

For U.S. programs, the criteria for physicians who received all or part of their training outside of the United States is the same as for the Program Director. Written documentation of all training is required. The Accreditation Committee will review and the Board of Directors will approve that training is deemed equivalent to United States Boards.

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.

For JACIE accreditation purposes in Europe, the equivalent requirements include specialist registration or completion of higher specialist training in one of the specialties listed in B3.2.1. Where physicians received higher training outside of the U.S. or Europe, the JACIE Accreditation Committee will assess their documentation of training and the JACIE Board will make the final determination.

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.

The field of transplant medicine continues to evolve rapidly. Transplant physicians must participate regularly in educational activities related to the field. The program may define the quantity and type of continuing education that best suits the needs of its physicians. Evidence of compliance may include either formal or informal study, such as meets the requirements of AMA type I or II continuing education hours, or applicable national continuing education requirements. Presentation of CME lectures, papers at scientific meetings, or publication of manuscripts related to transplantation may also meet this standard.

STANDARD:

B3.4 TRAINING FOR CLINICAL PROGRAM DIRECTORS AND ATTENDING PHYSICIANS

B3.4.1 Adequate specific clinical training in HPC transplant medicine shall be defined as a minimum of a one year experience in the management of transplant patients in both inpatient and outpatient settings.

B3.4.2 Clinical Programs transplanting pediatric patients shall have physicians experienced in treating pediatric patients as defined in B3.1.3.

B3.4.3 Clinical training and competency shall include the management of:

B3.4.3.1 Autologous transplant patients for physicians in Clinical Programs requesting accreditation for autologous transplantation.

B3.4.3.2 Allogeneic transplant patients for physicians in Clinical Programs requesting accreditation for allogeneic transplantation.

B3.4.3.3 Both autologous and allogeneic transplant patients for physicians in Clinical Programs requesting accreditation for autologous and allogeneic transplantation.

B3.4.4 Physicians in Clinical Programs requesting accreditation for autologous and/or allogeneic transplantation shall have specific training and competency in each of the following areas:

B3.4.4.1 Indications for HPC transplantation

B3.4.4.2 Selection of appropriate patients and preparative high dose therapy regimens

B3.4.4.3 Pre-transplant patient evaluation, including assessment of appropriate patient eligibility and HPC adequacy with respect to collection

B3.4.4.4 Administration of high-dose therapy

B3.4.4.5 Administration of growth factors for HPC mobilization and for post-transplant hematopoietic cell reconstitution

B3.4.4.6 Management of neutropenic fever

B3.4.4.7 Diagnosis and management of infectious and non-infectious pulmonary complications of transplantation

B3.4.4.8 Diagnosis and management of fungal disease

B3.4.4.9 Diagnosis and management of veno-occlusive disease of the liver

B3.4.4.10 Management of thrombocytopenia and bleeding

B3.4.4.11 Management of hemorrhagic cystitis

B3.4.4.12 Management of nausea and vomiting

B3.4.4.13 Management of pain

B3.4.4.14 Management of terminal care patients

B3.4.4.15 Documentation and reporting for patients on investigational protocols

B3.4.4.16 Diagnosis and management of HPC graft failure

B3.4.5 Specific clinical training and competency in each of the following additional areas required for physicians in Clinical Programs requesting accreditation for allogeneic hematopoietic cell transplantation shall include:

B3.4.5.1 Identification and selection of HPC source, including use of donor registries

B3.4.5.2 Methodology and implications of human leukocyte antigen (HLA) typing

B3.4.5.3 Management of patients receiving ABO incompatible HPC products

B3.4.5.4 Diagnosis and management of cytomegalovirus (CMV) infection and disease

B3.4.5.5 Diagnosis and management of other viral infections in immunocompromised hosts

B3.4.5.6 Diagnosis and management of acute and chronic graft versus host disease

B3.4.5.7 Diagnosis and management of post-transplant immunodeficiencies.

B3.4.5.8 Evaluation of chimerism

GUIDANCE:
The minimal documentation required to comply with this standard is a letter from each of the Directors of the Programs, departments and/or institutions where this training and/or 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 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 and competency in each of the cognitive and procedural skills listed in sections B3.4.3 - B3.4.7. Alternatively, the Program Director can submit documentation of at least two years experience as attending physician in the U.S. or consultant/senior physician in Europe or Australasia, responsible for the clinical management of HPC recipients in both the inpatient and outpatient settings. Written evidence may include letters from division/department heads.

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 Program Director. This can be in the form of a letter, checklist, or description of the number of times the physician has handled the particular situation. If the physician has published any articles relating to the issue, a copy of the publication will serve as documentation.

STANDARD:

B3.4.6 The HPC transplant physicians shall be proficient in the HPC product infusion.

GUIDANCE:
This requirement for proficiency in infusion may be documented with copies of infusion reports for each physician or by competency evaluations developed by the program.

STANDARD:

B3.4.7 The HPC transplant physicians shall be knowledgeable in the following procedures:

B3.4.7.1 HPC processing

B3.4.7.2 HPC cryopreservation

B3.4.7.3 Bone marrow harvest procedures

B3.4.7.4 Apheresis procedures

GUIDANCE:

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 (red cell depletion, T-cell depletion, 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). That each physician is knowledgeable needs to be documented, using a letter from the Program Director, evidence of CME or a copy of a publication.

The increase in use of peripheral blood hematopoietic progenitors has been associated with a proportional decrease in the number of marrow harvests performed. Some programs use peripheral blood exclusively as a source of hematopoietic progenitors. Accordingly, it is not necessary for every physician to be specifically trained or competent to collect marrow (although each program must have access to at least one physician who is trained and competent in bone marrow harvesting (standard B3.1.5 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.

STANDARD:

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

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

B3.5.2 Mid-level practitioners shall be trained and competent specifically in the transplant-related cognitive and procedural skills that they routinely practice. These skills may include but are not limited to those listed in B3.4.3 - B3.4.5.

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

GUIDANCE:

Evidence of current licensure to practice in the jurisdiction of the transplant program as well as a written description of responsibilities with description of supervision should be presented. Competency in each of the areas described in sections B3.4.3 - B3.4.5, as applicable to the cognitive and procedural skills they routinely practice, must be documented for each Mid-Level Practitioner by the Program Director. This can be in the form of a letter, checklist, or competency evaluation.

All mid-level practitioners should have documentable continuing education annually. When conferences

or courses attended cover the subjects in B3.4.3 - B3.4.5 or other relevant aspects of hematopoietic progenitor cell therapy, documentation of such continuing education could be used to support training and competency.

STANDARD:

B3.6 CONSULTING PHYSICIANS

B3.6.1 The Clinical Program shall have access to board certified/eligible (or non-U.S. equivalent) consulting physicians from key disciplines who are capable of assisting in the management of patients requiring medical care, including but not limited to:

B3.6.1.1 Surgery

B3.6.1.2 Pulmonary medicine

B3.6.1.3 Intensive care

B3.6.1.4 Gastroenterology

B3.6.1.5 Nephrology

B3.6.1.6 Infectious disease

B3.6.1.7 Cardiology

B3.6.1.8 Pathology

B3.6.1.9 Psychiatry

B3.6.1.10 Radiation oncology with experience in large-field (e.g., total body or total lymphoid) irradiation treatment protocols, if radiation therapy is administered

B3.6.2 A Clinical Program treating pediatric patients shall have consultants, as defined in B3.6.1, qualified to manage pediatric patients.

GUIDANCE:

The standard requires that consulting physicians be available. There must be at least one for each specialty. If a group of physicians is available to assist in the management of transplant patients, the applicant facility can list and document one member of that group and state that the entire group practice participates. Written 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. Transplant programs shall have physicians on the team who demonstrate age-specific expertise in the age ranges transplanted by the program (B3.6.2 applies).

STANDARD:

B3.7 NURSES

B3.7.1 The Clinical Program shall have nurses and nurse supervisors formally trained and experienced in the management of patients receiving HPC transplants.

B3.7.2 A Clinical Program treating pediatric patients shall have nurses formally trained and experienced in the management of pediatric patients.

B3.7.3 Training shall include hematology/oncology patient care; administration of high-dose therapy, growth factors, and immunosuppressive medications; management of infectious complications associated with compromised host defense mechanisms; administration of blood products; and an appropriate degree of intensive medical/pediatric nursing care.

B3.7.4 There shall be written policies for all relevant nursing procedures, including, but not limited to, infection prevention and control, administration of the preparative regimen, transplantation of HPC, central venous catheter care, blood product transfusion, and transplant nurse competency evaluation process.

GUIDANCE:

These are core competencies for nurses in hematopoietic progenitor cell transplantation. Formal training can include in-services and annual review classes that address these topics, conferences attended, or on-the-job training. All of these should be documentable with a conference attendance document, 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. It is important for nurses in units that care for patients to be oriented to the special needs of these patients. For example, 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. Evidence of training in these core competencies must be documented. 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 transplant teams are 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. 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.

Not all nurses will have had specific transplantation training as part of their formal job orientation. Some nurses may have been able to travel to another transplant institution for specific training. Because on-going education and documentation of continued competency are recommended, the inspector may ask to review documentation of in-service training and/or attendance at conferences.

STANDARD:

B3.8 SUPPORT SERVICES STAFF

B3.8.1 The Clinical Program shall have one or more designated staff to assist in the provision of appropriate pre-transplant patient evaluation, treatment, and post-transplant follow-up and care.

B3.8.2 The Clinical Program shall have pharmacy staff knowledgeable in the use and monitoring of pharmaceuticals used by the Clinical Program.

B3.8.3 The Clinical Program shall have 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.

B3.8.4 There shall be appropriate Social Services staff.

B3.8.5 There shall be appropriate Physical Therapy staff.

B3.8.6 There shall be Data Management staff sufficient to comply with Section B9.

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

B4 QUALITY MANAGEMENT

STANDARD:

B4.1 The Clinical Program shall have a written Quality Management Plan that addresses, at a minimum:

- *B4.1.1 Organizational structure*
- *B4.1.2 Process development and review*
- *B4.1.3 Personnel qualifications, training, and competency*
- *B4.1.4 Agreements*
- *B4.1.5 Outcome analysis*
- *B4.1.6 Audits*
- *B4.1.7 Management of cellular therapy products with positive microbial culture results*
- *B4.1.8 Detection and reporting of errors, accidents, and adverse events*
- *B4.1.9 Record review and document control*
- *B4.1.10 Product tracking*

GUIDANCE:
Development of a comprehensive Quality Management (QM) Program is often the most challenging and time-consuming exercise that the Transplant 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 facility will implement its quality assurance, control, assessment, and improvement activities. The QM Plan does not necessarily need to be stand-alone, serving only the Transplant Program. For example, the Clinical Program 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 Transplant Program may have one QM Plan that addresses all aspects of the Clinical, Collection, and Processing facilities. There should also be a provision for communication of information between key elements of the Transplant Program, including vendors and collaborators. Free-standing facilities will have individual QM Plans, but all elements listed are required.

STANDARD:

B4.2 The Clinical Program Director shall be responsible for the Quality Management Plan as it pertains to the Clinical Program. The performance of this activity may be delegated to a designated individual(s) with appropriate training, knowledge, and expertise.

B4.2.1 The designated individual(s) shall have authority over and responsibility for ensuring that the Quality Management Plan is effectively established and maintained.

B4.2.2 The designated individual(s) shall not have oversight of his/her own work if this person also performs other tasks in the Clinical Program.

B4.2.3 The designated individual(s) shall report on quality management activities, at a minimum, quarterly.

B4.2.3.1 The results of Quality Management activities shall be reviewed and approved by the Clinical Program Director.

B4.2.4 The designated individual(s) shall provide a report on the performance of the Quality Management Plan, at a minimum, annually to the Clinical Program Director.

B4.2.5 There shall be an overall Clinical Program Quality Management Program that incorporates the information from clinical, collection, and processing facility quality management.

GUIDANCE:
There must be a designated person to oversee the QM Program. The ultimate responsibility for performance of the quality plan and monitoring of all program elements, internal or contracted, will fall to the Transplant Program Director. If the Transplant Program Director differs from the Clinical Program Director (e.g., an adult unit director and a pediatric unit director), the latter individual may be designated as the having responsibility for review and management of errors, accidents and adverse events as indicated.

The day-to-day tasks of the QM Program, however, may be delegated to an individual within the program with sufficient expertise. This person 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 Transplant Program; or it could be a member of the transplant team. However, the designated person must have sufficient knowledge and training to facilitate the identification of improvement opportunities by the staff. 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. The same person may be responsible for QM of all components of the 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.

STANDARD:
B4.3 The Quality Management Plan shall include an organizational chart of key personnel and functions within the Clinical Program.

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

GUIDANCE:
The organizational chart should include the reporting structure for the Transplant Program; organizational charts for matrix programs should reflect the sphere on influence of individuals rather than just the lines of legal authority. The description of the operation of the quality program should include the mechanisms (meetings), participants, schedule, and documentation. 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 program.

STANDARD:

B4.4 The Quality Management Plan shall include policies and procedures for development and implementation of written agreements with third parties whose services impact the cellular therapy product.

GUIDANCE:

This standard is more likely to apply to the processing or collection facilities. However, if the Clinical Program interacts with third parties for provision or testing of cellular therapy products, it should 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, should be reviewed and renewed on a regular basis, and should include provision for the maintenance of records following termination of the agreement.

STANDARD:

B4.5 The Quality Management Plan shall include methods for process development, approval, implementation, review, revision, and archiving for all critical processes, policies, and procedures.

B4.5.1 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 and preventive action.

GUIDANCE:

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, outcomes analyses, training records, etc. The QM Program needs to identify the documents critical to the Transplant 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. The inspector will look to see how the program controls modifications of documents and whether retrospective review is possible.

Quality management 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 program should develop and prioritize performance measures. These may include, for example, survival, treatment-related mortality, specific complication rates, and other clinical outcomes, as well as adherence to selected policies or procedures. 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. 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. Some required performance parameters are listed in B9.2.

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. 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.

STANDARD:

B4.6 The Quality Management Plan shall include personnel requirements for each key position in the Clinical Program. Personnel requirements shall include at a minimum:

B4.6.1 A system to document the following for all medical, nursing, and pharmacy staff:

B4.6.1.1 Initial qualifications and training

B4.6.1.2 Annual performance review

B4.6.1.3 Provisions for continuing education

GUIDANCE:

The QM Plan 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 Transplant Program. Documentation of training should include all cognitive and procedural skills dictated by these standards as is relevant to each individual.

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 competency and annual continued competency may be assessed by observation, the use of written tests, and successful completion of proficiency surveys. Procedures for personnel training and competency assessment must be defined by an SOP (See B5.1.14 and B5.1.15). 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 training plan SOP should also define the minimal qualifications of any designated trainers.

STANDARD:

B4.7 The Quality Management Plan shall include a process for documentation and review of outcome analysis and product efficacy, as appropriate, including at least:

B4.7.1 For HPC products, a process for documentation and review of time to engraftment following product administration.

GUIDANCE:
Outcome analysis involves the collection, evaluation, and analysis of engraftment data. Ordinarily, engraftment is monitored for total nucleated cells or neutrophil and for platelets. Each Transplant Program should define the engraftment criteria that they deem acceptable. 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 transplant facility. The inspector will ask to see 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.

STANDARD:

B4.8 The Quality Management Plan shall include a process and timetable for conducting independent quality audits of the Program's activities to verify compliance with elements of the Quality Management Program.

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

B4.8.2 Audit results shall be reviewed, reported, and documented, at a minimum, on a quarterly basis.

B4.8.3 The results of audits shall be used to recognize problems, detect trends, and identify improvement opportunities.

GUIDANCE:
There is an emphasis on audits in section B of the FACT-JACIE Standards because of the recognition of the difficulty of validating clinical processes. 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 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 Program Director.

Examples of audits in the Clinical Program include:

a) Adherence to policies and procedures (i.e., chemotherapy administration or patient/donor selection)
b) Timely distribution of correctly written medical orders (i.e., for collection, processing, and infusion of cells)
c) Turn-around time for laboratory results
d) Incidence of nosocomial systemic infections

The term "independent" when applied to audits does not mean that the auditor must be external to the program, but that he or she should not have performed the actions being audited. Some larger programs may have a designated position for an individual who performs such audits, but in smaller programs it is possible to use a team member who has sufficient expertise. For example:

1) If the program elected to audit donor eligibility determinations and that task was normally performed by outpatient clinic staff, the audit could be performed by an inpatient nurse.
2) In a joint adult and pediatric program, pediatric staff could audit functions performed by the adult team and vice versa.

The inspector should expect to find a written plan, assessment and audit results, actions taken, and follow-up assessments and audits. Required audits are listed in B9.2. Review by the Clinical Program

Director is to be documented. Documentation of the results and review of these audits will be requested by the inspector.

There should be evidence that audit reports are shared with the Clinical staff, and the Medical Director as appropriate, the Program Director, Laboratory, and others with potential interest. The inspector should review the audit process and example audits to determine 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.

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.

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).

STANDARD:

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

B4.9.1 Documentation and product labeling.

B4.9.2 Release of the product from the distribution facility, including identification of authorized individuals and criteria for product release.

B4.9.3 Investigation of cause.

B4.9.4 Notification of transplant physician, Collection Facility and/or Cell Processing Facility as applicable.

B4.9.5 Notification of the recipient prior to infusion.

B4.9.6 Recipient follow-up and outcome analysis.

B4.9.7 Follow-up of the donor, if relevant.

B4.9.8 Reporting to regulatory agencies if appropriate.

GUIDANCE:

The Transplant Program must develop an integrated approach to the management of cellular therapy products with positive microbial culture results that are identified either before or after the products have been infused. Policies and procedures are required in all three areas of the transplant program – clinical, collection, and laboratory. These Standards list the topics that must be addressed in policies, but do not dictate a single policy that must be followed.

The program should have policies that address how they 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. In the U.S., regulations for 351 and 361 products should be followed and the 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 program should have policies that cover timely notification of the transplant physician caring for the patient as well as the collection and cell processing facilities. The inspector may ask to see the chart of a patient or donor where the cellular therapy product was contaminated and review how the program managed the process.

STANDARD:

B4.10 The Quality Management Plan shall include a system for detecting, evaluating, documenting, and reporting errors, accidents, suspected adverse events, biological product deviations, and complaints.

B4.10.1 Documentation of each adverse event that occurs in the Clinical Program shall be reviewed by the Clinical Program Director as appropriate.

B4.10.2 Adverse events in the Clinical Program shall be documented in a manner that complies with institutional requirements and applicable governmental laws and regulations.

B4.10.3 Deviations from key Standard Operating Procedures (B5.1.1, B5.1.7, B5.1.8) shall be documented.

B4.10.3.1 Planned deviations shall be pre-approved by the Clinical Program Director or designee.

B4.10.3.2 Unplanned deviations and associated corrective actions shall be reviewed by the Clinical Program Director or designee.

B4.10.4 Corrective actions shall be implemented, as appropriate.

B4.10.5 Effectiveness of corrective actions shall be verified.

B4.10.6 A written description of adverse events shall be made available to the recipient's and/or donor's physician and the collection and processing facilities, if appropriate.

B4.10.7 When applicable, the event shall be reported to the appropriate regulatory agencies.

B4.10.8 There shall be policies and procedures to document and follow up customer-reported product failures, concerns, or complaints.

GUIDANCE:

There must be a mechanism 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 (See B5.1.11 and B5.1.12) along with when and how each is reported.

There must be a mechanism to 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 program is expected to comply with institutional requirements and applicable governmental regulations pertaining to the reporting of adverse events in the Clinical Program. Each program should define errors, accidents, deviations, and adverse reactions, along with when and

how each are reported. The following are examples of adverse events that must be reported: adverse events involving the transmission of communicable disease, product contamination or failure of engraftment, 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.

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.

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.

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.

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 Program Director. The inspector should ask to see SOPs that describe how adverse reactions are investigated and reported, files of adverse reactions, and evidence that adverse reactions are reviewed by the Program Director and reported to the transmitting facility and appropriate governmental agencies.

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 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. EU Commission Directives 2006/17/EC and 2006/86/EC include equivalent requirements for non-conforming products. The QM Program should address how the 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 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.

STANDARD:

B4.11 The Quality Management Plan shall include a mechanism for document control and for the regular review of records relating to HPC transplantation and cellular product infusion. The document control system shall include at a minimum the following elements:

B4.11.1 Definition and current listing of all critical documents that must adhere to the document control system requirements.

B4.11.2 Assignment of a numeric or alphanumeric identifier to each document regulated within the system.

B4.11.3 A procedure for document approval, including the approval date, signature of approving individual(s), and the effective date.

B4.11.4 A system to ensure that controlled documents cannot undergo accidental or unauthorized modification.

B4.11.5 A system for documentation of training associated with each procedure and its revisions.

B4.11.6 A system for document change control that includes a description of the change, the signature of approving individual(s), approval, date, and effective date.

B4.11.7 A system for the retraction of obsolete documents to prevent unintended use.

B4.11.7.1 Obsolete documents shall be archived for a minimum of ten (10) years.

B4.11.8 A system for record creation, assembly, storage, archival, and retrieval.

GUIDANCE:

The Quality Management Plan should provide details on how the program deals with document control. It should list which documents are considered critical and fall under the purview of the document control system. For example, in B5.1 the program shall have an SOP for Infusion of HPCs, so this would be considered a critical document. It is recognized that the practice of medicine may require some flexibility and the program may choose to have guidelines for clinical care issues such as antibiotic therapy that would not be considered critical documents. The program should also have systems to ensure documents cannot be modified and are archived. Further guidance on these issues is provided in Section 5.

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

STANDARD:

B4.12 The Quality Management Plan shall include a process for product tracking that allows tracking from the donor to the recipient or final distribution and from the recipient, or final disposition, to the donor.

GUIDANCE:
One of the most important paper trails in the Transplant 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 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.

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, outcomes analyses, training records, etc. The QM Program needs to identify the documents critical to the Transplant 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. The inspector will look to see how the program controls modifications of documents and whether retrospective review is possible.

STANDARD:
B4.13 The Quality Management Plan shall include a mechanism to ensure continuous operations in the event that the Clinical Program's computer system ceases to function, including a plan for data backup and a mechanism to ensure compliance with applicable laws.

GUIDANCE:
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 hospital 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 ensure 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.

B5 POLICIES AND PROCEDURES

STANDARD:
B5.1 The Clinical Program shall have documented policies and procedures addressing all appropriate aspects of operations and management including, at a minimum:

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

B5.1.2 Donor consent

B5.1.3 Patient consent

B5.1.4 Emergency and safety procedures

B5.1.5 Donor and patient confidentiality

B5.1.6 Infection prevention and control

B5.1.7 Administration of the preparative regimen

B5.1.8 Transplantation of hematopoietic progenitor cells

B5.1.9 Blood product transfusion

B5.1.10 Quality management and improvement

B5.1.11 Errors, accidents, and adverse events

B5.1.12 Biological product deviations

B5.1.13 Corrective actions

B5.1.14 Personnel training

B5.1.15 Competency assessment

B5.1.16 Outcome analysis

B5.1.17 Audits

B5.1.18 Facility maintenance and monitoring

B5.1.19 Disposal of medical and biohazard waste

B5.1.20 Disaster response

GUIDANCE:
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. The items in the checklist include the minimum requirements. In those circumstances where program or institution standards vary from the 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. 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 initial and annual review and approval of revisions within 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 procedure manual must be identical to the source document and must not be used to alter, modify, extend, delete or otherwise edit any SOP. This should be verified by 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. The inspector should verify the procedure for development and review for all policies and procedures.

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.

The SOP for Quality Management should provide information on how the clinical program conducts clinical quality management activities to ensure they meet all the standards outlined in B4. It is acceptable to refer to the host institution's overall quality plan if the program uses that plan to meet some of the standards outlined in B4.

It is recognized that the practice of medicine requires some flexibility and the program may choose to designate policies for some clinical care practices as practice guidelines rather than critical document SOPs to allow this. For example, in a guideline for the use of antibiotics for fever, the program may wish 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:

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

B5.2.1 A procedure for preparation, approval, implementation, review, and revising all procedures.

B5.2.2 A standardized format for procedures, including worksheets, reports, and forms.

B5.2.3 A system of numbering and/or titling of individual procedures, policies, worksheets, and forms.

GUIDANCE:

The SOP manual must have a Standard Operating Procedure outlining the method by which the Clinical Facility creates, approves, implements, reviews, and updates its SOPs (the "SOP for SOPs"). 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 Facility 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. 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 "SOP for SOPs" adheres to the requirements for all controlled documents as specified in standard B4.11. 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 facility's standard SOP format.

STANDARD:

B5.3 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 of the procedure.

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, including diagrams and tables as needed.

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.

B5.3.7 Documented approval of each procedure and procedural modification by the Clinical Program Director or designated physician prior to implementation and annually thereafter.

B5.3.8 Copies of current versions of orders, worksheets, reports, labels, and forms, where applicable.

GUIDANCE:
This Standard defines the minimum elements required in each SOP. 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 somewhere.

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 CLSI Website. The CLSI format is not required. The facility may use the format of its choice, as long as all listed elements are present. Some 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) or from the Canadian Standards Association website (www.csa-international.org).

Although the FACT-JACIE Standards indicate that an individual designated by the director may review procedures on an annual basis, the director remains ultimately responsible for this process. The designated individual should be qualified to review SOPs.

Copies of 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 may be prudent to attach one or more completed forms to illustrate possible real life scenarios. Although not required by FACT-JACIE 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.

STANDARD:
B5.4 Copies of the Standard Operating Procedures Manual shall be readily available to the facility staff at all times.

GUIDANCE:
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 transplant 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 transplant program. The inspector should verify the procedure for the development and approval of SOPs, implementation, revision, and archiving of SOPs. Copies of current versions of orders, 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. It may be prudent to attach one or more completed forms to illustrate possible "real-life" scenarios.

STANDARD:
B5.5 All personnel in the facility shall follow the Standard Operating Procedures.

B5.6 New and revised policies and procedures shall be reviewed by the staff prior to implementation. This review and associated training shall be documented.

GUIDANCE:
Personnel are required to adhere to the approved SOPs in their manual. Although only annual review is required, when conditions require that a procedure or practice be modified, SOP review and revision must occur in a timely fashion. Documentation that staff have reviewed new and revised procedures and received appropriate training before the procedures are implemented should be reviewed by the inspector. 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 implementation. Training guides specific to each procedure and to any major revision also facilitate documentation of appropriate training of staff.

STANDARD:
B5.7 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.

GUIDANCE:
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. The inspector should review the SOP archival system, including local requirements.

STANDARD:
B5.8 All Standard Operating Procedures shall comply with these Standards and all applicable governmental regulations.

GUIDANCE:
While the Clinical Facility is expected to adhere to their own operating procedures, those procedures must be in compliance with these Standards and with applicable governmental regulations. A more stringent local standard is acceptable, but not one that contradicts FACT or governmental requirements.

STANDARD:

B5.9 There shall be a process to address age specific issues in the Standard Operating Procedures, as appropriate.

GUIDANCE:

Pediatric transplant patients and donors require specific policies and procedures that address issues of age and size of the donor. Any program that ever 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. 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 SOP Manuals.

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, and consideration should be given to providing the opportunity for younger donors to sign "assent" to donate.

B6 DONOR SELECTION, EVALUATION, AND MANAGEMENT

STANDARD:

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

B6.2 There shall be donor evaluation procedures in place to protect the safety of the cellular product donor.

B6.2.1 The donor shall be evaluated for potential risks of the collection procedure, including:

B6.2.1.1 Possible need for central venous access and/or mobilization therapy for collection of peripheral blood cells.

B6.2.1.2 Anesthesia for collection of marrow.

B6.2.2 The risk of donation and informed consent shall be documented.

B6.2.3 The use of a donor who does not meet the Clinical Program donor safety criteria shall require documentation of the rationale for his/her selection by the transplant physician.

B6.2.4 Issues of donor health that pertain to the safety of the collection procedure shall be communicated in writing to the Collection Facility staff.

GUIDANCE:

Sections B6.1 through B6.7 apply to both allogeneic and autologous donors. They 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 Section B6.8 to ensure appropriate histocompatibility matching and to protect the recipient from the risks of transmissible disease.

These standards cover the requirements for donor identification, evaluation, selection, and management. The transplant 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. For donors of cellular and tissue-based products, the Food and Drug Administration, or non-U.S.

equivalent 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 xenotransplantation, and 3) tests negative or non-reactive for relevant communicable disease agents within the specified time frame for the product. In addition, this Standard requires that the transplant program identify the institutional criteria for donor medical suitability and donor selection. 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.

These standards also require that if chosen donors are ineligible according to FDA regulation 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 by the transplant physician of urgent medical need for the 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 summary of records 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 biohazard legend for cellular 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 the FACT-JACIE Standards Appendix 1.

The inspector should verify that policies and SOPs for donor selection 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.

STANDARD:

B6.3 There shall be donor evaluation procedures in place to protect the recipient from the risk of disease transmission from the donor.

B6.3.1 There shall be procedures for all steps in screening, testing, and determining donor eligibility, and for all regulatory requirements related to cellular therapy donors.

B6.3.2 Within thirty (30) days prior to collection, all HPC donors shall be tested for evidence of clinically relevant infection by the following communicable disease agents:

B6.3.2.1 Human immunodeficiency virus, type 1

B6.3.2.2 Human immunodeficiency virus, type 2

B6.3.2.3 Hepatitis B virus

B6.3.2.4 Hepatitis C virus

B6.3.2.5 Human T-cell lymphotropic virus I (per governmental regulations)

B6.3.2.6 Human T-cell lymphotropic virus II (per governmental regulations)

B6.3.2.7 Treponema pallidum (syphilis)

B6.3.3 Additional tests shall be performed as required to assess the possibility of transmission of other infectious or non-infectious diseases.

B6.3.4 For viable, lymphocyte rich cells, including therapeutic cells, each donor shall be tested for communicable disease agents listed in section B6.3.2 within seven (7) days prior to or after collection, or in accordance with applicable governmental regulations.

GUIDANCE:
Standards included under B6.3 define the minimal evaluation for infectious agents. This applies to autologous donors as well as allogeneic donors. Assessment of all donors is required to minimize the risk of transmitting infection to the recipients as well as to prevent risk of contamination of staff or cross-contamination of other HPC during collection or processing /storage. The FDA regulation also specifies that the donor sample for infectious disease testing must be obtained within 30 days of donation for peripheral blood stem cells and within seven days of donation for other leukocyte-rich cellular products. The EU regulations adopt the same requirements for donor lymphocytes (DLI) as for HPC, i.e., testing for both HPC and lymphocyte donors must be within 30 days prior to donation. Testing must occur in accordance with written SOPs and using appropriate FDA-licensed, approved, or cleared donor-screening tests in accordance with the manufacturer's instructions, or non-U.S. equivalent. The results of donor eligibility determination must be recorded.

These standards detail minimal laboratory testing. All laboratory tests must be performed by an accredited laboratory as is relevant for the tests (e.g., CLIA, CAP, ASHI, ABBB, JCAHO, HCFA, etc.).

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 collection of other leukocyte-rich cellular products or as required by applicable regulations.

The inspector should verify that 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. The rationale and informed consent from the donor and recipient should be documented for donors with positive results. The inspector must verify that the donor eligibility determination is recorded.

Other communicable disease tests should be added to the donor evaluation as they become available and recommended to increase the product safety. According to the FDA, there are other relevant communicable diseases besides those specifically listed in the regulations. FDA intends to notify the transplant industry through published guidance from time to time of those additional relevant communicable diseases. 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 either to the recipient or to the staff handling the product because the disease or disease agent:
  - It is transmissible through HCT/P
  - It is sufficiently prevalent as to effect the potential donor population
- There could be fatal or life-threatening consequences as a result of transmission
- There have been developed effective screening mechanisms and/or an approved screening test for donor specimens.

Relevant communicable diseases not specifically listed in the regulation as of August 2007 are:

- West Nile Virus (screening and testing available)
- Sepsis (screening available)

- Vaccinia (screening available)

See FDA Guidance Document ("Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Product [HCT/Ps], 2007) at www.fda.gov/cber/guidelines.htm for additional information.

Testing for West Nile Virus is not currently mandated by the 3rd edition of the FACT-JACIE Standards. However, Standards do require testing for anything determined by regulatory authorities to be relevant communicable disease. 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. Due to the immunocompromised status of HPC recipients, it may be agreed that it is beneficial to perform West Nile Virus testing of allogeneic and autologous donors, at least in regions of the world where WNV has been reported. This would include the U.S. 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. In the event that West Nile Virus testing is performed, the method of testing, the facility performing the testing, interpretation of test results, and actions taken, based on test results, should be clearly outlined in written SOPs.

STANDARD:

B6.4 Any abnormal findings shall be reported to the prospective donor with documentation in the donor record of recommendations made for follow-up care.

GUIDANCE:

Abnormal findings in a donor, including but not limited to the testing results, may have important implications for the donor, 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. These actions should be documented in the donor's medical record. The inspector should verify that this documentation is present when indicated. 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 programs.

STANDARD:

B6.5 All donors shall be tested for ABO group and Rh type.

B6.5.1 Allogeneic donors shall be tested for ABO group and Rh type on each day of collection.

B6.5.2 Autologous donors shall be tested for ABO group and Rh type at least on the first day of collection.

B6.6 A pregnancy assessment shall be performed for all female donors of childbearing potential within seven (7) days prior to initiation of recipient's conditioning regimen or of donor starting mobilization regimen.

B6.7 Laboratory testing on all donors shall be performed by a laboratory accredited or licensed in accordance with applicable U.S. or non-U.S. equivalent regulations using one or more donor screening tests approved or cleared by the FDA or non-U.S. equivalent.

GUIDANCE:

These standards detail minimal laboratory testing. All laboratory tests must be performed by an accredited laboratory as is relevant for the tests (e.g., CLIA, CAP, ASHI, ABBB, JCAHO, HCFA, etc.). 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 cell product and within 7 days for leukocyte rich product prior to the collection as required by United States FDA or as required by non-U.S. equivalent regulations.

The donor and recipient's ABO group and RH type should be determined and documented prior to the collection of hematopoietic progenitor cells from marrow or peripheral blood. There should be documentation in the medical record of these results prior to initiating the collection process. The testing and documentation should occur according to written SOPs. SOPs to manage ABO and Rh mismatches between the donor and recipient should be established and verified by the inspector.

Pregnancy assessment is required since the donation of hematopoietic progenitor cells from marrow or peripheral blood and anesthesia may pose a risk to the fetus. Assessment may include a pregnancy test, but a test is not required. 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 inspector should verify that ABO and Rh typing and pregnancy tests are performed according to the standard.

The inspector should also verify that there is documentation in the medical record that prospective donors were informed of the abnormal findings including recommendations for work-up, treatment, and follow-up.

STANDARD:

B6.8 ALLOGENEIC DONORS

B6.8.1 In addition to laboratory testing for relevant communicable disease agents as defined in B6.3.2, allogeneic donors shall be evaluated for risk factors for disease transmission by medical history, examination of relevant medical records, and physical examination.

B6.8.2 The medical history shall include at least the following:

B6.8.2.1 Vaccination history

B6.8.2.2 Travel history

B6.8.2.3 Blood transfusion history

B6.8.2.4 Questions to identify persons at high risk for transmission of communicable disease as defined by the FDA or non-U.S. equivalent

B6.8.2.5 Questions to identify persons at risk of transmitting inherited conditions

B6.8.2.6 Questions to identify persons at risk of transmitting a hematological or immunological disease

B6.8.2.7 Questions to identify a past history of malignant disease

B6.8.3 Allogeneic donors shall be tested for Cytomegalovirus (unless previously documented to be positive).

B6.8.4 Allogeneic donors shall be tested at a minimum for HLA-A, B, DR type by a laboratory accredited by ASHI, EFI, or an affiliate.

B6.8.5 Allogeneic donors shall be tested for red cell compatibility where appropriate.

B6.8.6 Allogeneic donor eligibility, as defined by FDA donor eligibility regulation or non-U.S. equivalent governmental regulation, shall be determined by a physician and shall be documented in the recipient's medical record before the recipient's high dose therapy is initiated and before the donor is mobilized.

B6.8.7 The use of an ineligible allogeneic donor shall require an urgent medical need documentation, including the rationale for his/her selection and suitability by the transplant physician, and the documented informed consent of the donor and the recipient.

B6.8.8 Allogeneic donor eligibility and suitability shall be communicated in writing to the collection and cell processing facilities.

B6.8.9 The donor shall confirm that all the information provided is true to the best of his/her knowledge.

GUIDANCE:
These standards are meant to require the Medical 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.

FACT-JACIE standards and the FDA require that all donors be screened by medical history and risk factors for human transmissible spongiform encephalopathy, Creutzfeldt-Jakob disease, 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 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).

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 and measles. In those cases in which a potential donor has recently been vaccinated, both the reason for the vaccination and the time interval should be evaluated to estimate the potential risk to a recipient. There should be specific SOPs in dealing with donors who had received smallpox vaccination. Donors must be screened for traveling to the area that would put them at risk for malaria, human transmissible spongiform encephalopathy, SARS (severe acute respiratory syndrome) during periods of world-wide prevalence, or rare strains of HIV, which may not be detected by current screening tests.

Cytomegalovirus is considered to be a relevant communicable disease. 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 transplant program should have a clearly defined policy or procedure that addresses the use of CMV-seropositive donors.

STANDARD:

B6.9 DONOR CONSENT

B6.9.1 The collection procedure shall be explained in terms the donor can understand, and shall include information about:

B6.9.1.1 The significant risks and benefits of the procedure

B6.9.1.2 Tests performed to protect the health of the donor and recipient

B6.9.1.3 The rights of the donor to review the results of such tests

B6.9.1.4 Alternatives to donation

B6.9.1.5 Alternative modalities of donation

B6.9.2 The donor shall have an opportunity to ask questions and the right to refuse to donate.

B6.9.3 Informed consent from the donor shall be obtained and documented by a licensed physician or other health care provider familiar with the collection procedure.

B6.9.4 In the case of a minor donor, informed consent shall be obtained from the donor's parents or legal guardian in accord with applicable law and shall be documented.

B6.9.5 The allogeneic donor shall give informed consent and authorization in advance to release the donor's health information to the transplant physician and recipient as appropriate.

B6.9.6 Documentation of consent shall be available to the Collection Facility staff prior to the collection procedure.

GUIDANCE:

The essential elements of informed consent are that the donor, recipient or patient is told, in terms she or he 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, recipient, or patient 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 inspector may ask to see a consent form to ensure that all the required elements are in place and ask to see the clinic note which details discussion of the protocol. 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.

B7 THERAPY ADMINISTRATION

STANDARD:

B7.1 There shall be a written policy to ensure that the preparative regimen is administered safely.

B7.1.1 There shall be a written policy to ensure that chemotherapy is administered safely.

B7.1.1.1 The treatment orders shall include the patient height and weight, specific dates, daily doses (if appropriate), and route of each agent.

B7.1.1.2 Preprinted orders or electronic equivalent <u>should</u> be used for protocols and standardized regimens.

B7.1.1.3 The pharmacist preparing the chemotherapy shall verify the doses against the protocol or standardized regimen listed on the orders.

B7.1.1.4 Prior to administration of chemotherapy, two (2) persons qualified to administer chemotherapy shall verify 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.

GUIDANCE:

The inspector may ask to see generic policies and procedures and may also ask to see copies of treatment protocols in areas of patient care such as inpatient and outpatient units and pharmacy. The inspector may review the policies to confirm a policy for administration of chemotherapy. The inspector may also review specific patient charts to check that treatment orders and documentation are compliant with the guidelines and may ask if there have been any audits of compliance with these policies. While touring patient care areas, the inspector may also ask the pharmacist about their normal practice and ask nurses about the normal procedures for chemotherapy administration. The inspector may also ask staff members about their training in administering chemotherapy.

STANDARD:

B7.1.2 There shall be a written policy to ensure that radiotherapy is administered safely.

B7.1.2.1 There shall be a written request for radiotherapy including details of diagnosis, any prior radiotherapy that the patient has received, and any other factors that may increase the toxicity of radiotherapy.

B7.1.2.2 There shall be a consultation with a radiation therapist prior to initiation of therapy. The consult should include radiotherapy planning.

B7.1.2.3 Prior to administration of each dose of radiotherapy treatment, dose should be verified and documented as per radiation therapy standards.

B7.1.2.4 A final report of the radiotherapy details administered should be filed in the patient's records.

GUIDANCE:

Upon reviewing patients' charts, the inspector may ask to see the written request for the radiation therapy, the radiation consult, and radiation report at the end of treatment. In addition, the inspector may look at documentation that the radiation was given on a specific date, and its dose. The inspector may

also ask to see copies of treatment protocols that include radiation and verify it by comparing to patient charts.

STANDARD:

B7.2 There shall be a written policy to ensure safe administration of hematopoietic cell products.

B7.2.1 Two (2) qualified persons shall verify the identity of the recipient and the product prior to the infusion of the product.

B7.2.1.1 Verification of identity shall be documented.

B7.2.2 There shall be documentation in the patient medical record of the unit identifier and a copy of the distribution record (i.e. product infusion form).

B7.2.3 The Circular of Information for Cellular Therapy Products shall be available to staff.

GUIDANCE:

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. The inspector may ask clinical staff about their normal practice and ask to see copies of the current policies. The inspector can also ask staff members about their training in administration of hematopoietic cell products. They could also review specific patient charts 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 may also request to watch parts of the procedure.

B8 CLINICAL RESEARCH

STANDARD:

B8.1 If required by applicable regulations, Clinical Programs shall have formal review of investigational treatment protocols and patient consent forms by a mechanism that is approved by the Office for Human Research Protections under the Department of Health and Human Services, by the FDA, or by the equivalent agencies outside of the U.S., as applicable.

B8.1.1 Those programs utilizing applicable investigational treatment protocols shall have in place a pharmacy equipped for research activities, including a mechanism for tracking, inventory, and secured storage of investigational drugs.

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

GUIDANCE:

The purpose of these standards is to ensure that the program is obtaining appropriate review of clinical research protocols. The inspector may ask about the process for review of protocols, ask which IRB or non-U.S. equivalent is used by the program, and examine the Institutional Review Board (IRB) or non-U.S. equivalent regulatory binder for a specific study. In Europe, the Research Ethics Committee (REC) is the equivalent of the IRB in the U.S. The inspector could also ask to see a signed consent form in one of the patient charts and cross check approval dates with IRB or non-U.S. equivalent regulatory agency documents. The inspector should also ask if the center carries out any studies under Investigational New Drug (IND) or non-U.S. equivalent and, if appropriate, ask to see the regulatory binder for such studies.

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 their 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 at least the following elements 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.

GUIDANCE:

This standard aims to ensure that all the correct elements of informed consent are present for subjects treated on clinical research protocols. The inspector could ask to see the informed consent document in some of the charts they are reviewing and ensure that it is compliant with the Code of Federal Regulations (CFR) or non-U.S. equivalent requirements outlined in the checklist.

STANDARD:

B8.4 There shall be a mechanism in place to ensure, as appropriate, the financial disclosure of any issues that may represent a conflict of interest in clinical research.

GUIDANCE:

The purpose of this standard is to ensure that the program has a financial disclosure policy. The inspector may request the program's or institution's conflict of interest policy to ensure it is consistent with CFR Part 54 or other local regulatory requirements.

B9 DATA MANAGEMENT

STANDARD:

B9.1 The Program shall collect all the data contained in the Transplant Essential Data Forms of the CIBMTR or the Minimum Essential Data-A forms of the EBMT (See Appendix IV).

B9.2 Each transplant program shall periodically audit, at a minimum, the following data: patient outcomes, donor screening and testing, and recipient Day 100 treatment related mortality.

B9.2.1 Collection and analysis of data related to the audit shall be reviewed, reported, and documented, at a minimum, on an annual basis.

GUIDANCE:
To be consistent in the inspection and accreditation process, FACT and JACIE have developed standardized Inspection Report Forms to be utilized to determine if a 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 Transplant Essential Data (TED) or Minimal Essential Data (MED-A) forms are now included in the on-site inspection process to eliminate any ambiguity regarding the data elements to be collected. Although ten consecutive allogeneic and five consecutive autologous transplant recipients will be reviewed, the minimum number of data points to verify is thirty. However, the records and data points will be selected randomly to insure the highest quality of completeness and accuracy of the records reviewed.

The Program Director or designee will choose the patient charts to be reviewed, and list them on the inspection checklist. The ten consecutive allogeneic and five 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/MED-A forms. The Program Director or designee should also mark the location of primary records required to verify the data to facilitate the inspection process.

Data management obviously is an important element of good clinical care as well as clinical investigation. Data management will be evaluated during the on-site inspection by a review of representative patient records. The 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, 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/MED-A forms may be audited. Records will be assessed for accuracy by comparing the TED/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 purpose of selecting the 30 random data points and five required elements from appropriately selected patient records is to verify that:

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

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 even for smaller programs. The 30 data points constitute an arbitrary subset of information to be reviewed. If it is found in large part to be incorrect, it is likely that additional problems with record keeping would be found 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.

It is not the purpose of this chart review 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. However, the transplant program must furnish evidence of its own periodic data audits to evaluate patient outcomes as specified in standard B9.2. The choice of data to be audited is a

decision for the transplant program but should include engraftment, transplant related day 100 mortality, and donor screening and testing.

FACT and JACIE strongly recommend the publication of transplant data and strongly encourages the submission of transplant data to the CIBMTR and EBMT, as appropriate. Standard B9.1 does not require that transplant program data be submitted to these registries, however, it does require that all data collected in the TED/MED A form of the CIBMTR/EBMT be maintained by the transplant program.

In the event that the program does not submit data to these registries, it should provide reasonable explanations for not submitting the data. Standard B9.2, 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 forms currently utilized by the CIBMTR may be found on the organization's website at: www.ibmtr.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.

B10 RECORDS

STANDARD:

B10.1 Clinical Program records related to quality control, personnel training or competency, facility maintenance, facility management, or other general facility issues shall be retained in accordance with applicable laws or regulations, or a defined program or institution policy, unless otherwise specified in these Standards. Not all records need be immediately available.

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 governmental laws and regulations, but no less than 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 Employee records shall be maintained in a confidential manner and as required by applicable governmental laws and regulations.

GUIDANCE:

Each Clinical Program has the flexibility to develop individualized systems of maintaining and organizing records as long as certain objectives are achieved. 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. However, it is recommended that recent records should be kept on-site and archived records should be readily accessible within a reasonable time frame. The methods for filing and transfer of records to archival storage should be specified in the SOP manual. Records may be maintained electronically, as original paper records, photocopies, microfiche, or microfilm. Suitable equipment must be available for reading and/or photocopying records maintained on microfiche or microfilm. Electronic records must be backed up on a regular basis and stored to prevent their loss. The Clinical Program must make provisions for all records to be maintained for the required period in the event that the Clinical Program ceases operation.

Clinical Unit 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 3 years while records of facility maintenance may only need to be kept for a short time. It is suggested that programs have readily accessible records for, at least, quality control, personnel training and competency, for the last three years for inspector review. 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 standard 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 standard B3 (Personnel) including licenses and/or board certifications for all transplant and consulting physicians in other specialties, licenses for all midlevel 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 standard 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.

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 U.S. HIPAA regulations or equivalent non-U.S. laws or regulations on confidentiality and data protection. In Europe, the comparable law or regulation is EC 95/46 Directive. The inspector should be alert to breaches in policy 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. In European Union Member States, donor records required for full traceability must be maintained for a period of 30 years.

Data to be provided to other facilities involved in the collection or processing of the 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.

General Facility records include global policies for the entire institution of which the Clinical Unit is a part. These may include disaster plans, fire response and safety plans, biological, chemical and radiation disposal policies, and confidentiality requirements.

STANDARD:

B10.4 Research records shall be maintained in a confidential manner as required by applicable governmental laws and regulations, but no less than ten (10) years after the administration, distribution, disposition, or expiration of the cellular therapy product, whichever is latest.

GUIDANCE:

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, Institutional Review Board (U.S.)/Research Ethics Committee (Europe), and/or governmental authorities may place specific requirements for long-term maintenance of research records. The inspector should ask who is responsible for the research records, where the records are maintained, and determine if an organized system is in place that maintains patient confidentiality.

STANDARD:

B10.5 RECORDS IN CASE OF DIVIDED RESPONSIBILITY

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

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

GUIDANCE:

In the event that two or more facilities participate in the collection, processing or transplantation of a stem cell 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/tracking of relevant information to the correct source.

For example, programs that consist of pediatric and adult services at different hospitals may perform donor harvests at one facility that are used for a patient at another facility. An example would be if a child received a haploidentical transplant from a parent and the donors cells were collected at the adult hospital and then infused into the recipient at the pediatric hospital. Another example would be if a patient with NHL had autologous PBSC collected in first remission at one hospital and subsequently after relapse had an autologous transplant at a second hospital.

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. The inspector should determine if divided responsibility occurs regarding any aspect of the transplant process, and then ask to review a relevant patient file to confirm that an appropriate mechanism is in place to track the process from beginning to end.

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 the National Marrow Donor Program will have well defined procedures for divided responsibility. Where applicable, the HIPAA Final Rules or equivalent non-U.S. regulations should be followed. In the case of the National Marrow Donor Program, 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 product, transplant outcome data so far as it concerns the safety, purity, and potency of the product involved. The inspector should review the applicable SOPs regarding dissemination of transplant outcome data and verify that the process is in place. Minutes of Program Team Meetings and Quality Management Meetings provide one method of partial compliance with the standards as outlined in B10.

ACCREDITATION MANUAL – SECTION C
CELLULAR THERAPY PRODUCT COLLECTION STANDARDS

C1 GENERAL

STANDARD:

C1.1 These Standards apply to all HPC, Marrow; HPC, Apheresis; and other cellular therapy product collection activities performed within the Collection Facility.

GUIDANCE:

Section C describes the collection of hematopoietic-derived progenitor and therapeutic cells from marrow or peripheral blood for autologous, syngeneic or allogeneic transplantation and/or for research. Standards for the collection of hematopoietic progenitor cells (HPC) from umbilical cord blood, primarily for the purpose of banking, are found in the NetCord-FACT Standards (Third edition, 2007), which are specific to facilities providing this service. It is not the intent of these standards to address collection of alternative types of stem cells including, but not limited to, embryonic, pancreatic, muscular, mesenchymal or neuronal. Likewise, these standards do not apply to the procurement of mature blood cell products or plasma products collected and transfused for temporary support of patients with low blood counts.

STANDARD:

C1.2 The Collection Facility shall abide by all applicable governmental laws and regulations.

GUIDANCE:

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 program or facility to determine which laws and regulations are applicable. In some cases, regulations of governmental authorities outside of the jurisdiction of the Collection Facility may apply; for example, when a facility is sending or receiving cellular therapy products from outside of its immediate jurisdiction.

In the U.S., both HPC and Therapeutic Cell (TC) products 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) unless they are extensively manipulated, combined with a device, or their use is non-homologous, in which case 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. It is not the intent of these Standards to address processing of alternative types of stem cells including, but not limited to, embryonic, pancreatic, muscular, mesenchymal, or neuronal, which are exclusively regulated under GMP. Although many of the existing standards may be applicable to other types of cellular products, a facility cannot be cited for not following standards in cases where a deviation is recognized as limited to products other than marrow, peripheral blood progenitor cells (PBPC), or Therapeutic Cells.

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. Currently a new regulatory framework on advanced cell therapies is being proposed 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.

Compliance with any of the numerous U.S. federal and state regulations or equivalent international regulations [e.g., acceptable FDA audit, state licensure, licensing of tissue establishments by the Member State in the EU, Clinical Laboratory Improvement Act (CLIA), Occupational Safety and Health Administration (OSHA)], 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 accreditation body, should indicate that the Collection Facility is safely run and that the personnel are familiar with the principles of Good Laboratory Practice. However, compliance with other organization's standards or governmental regulations does not imply that FACT-JACIE Standards have been met. In all cases, governmental regulations supersede any organization's standards. The inspector should review current certifications to ascertain what areas of facility function have been certified by other organizations and/or competent authorities.

As part of the inspection process, the inspector may request review of documents indicating the Collection Facility is in compliance with governmental regulations. Such documents may include facility registration or licensure. Inspectors may also observe operations or procedures, and note if there are apparent practices that are not in compliance with regulations of OSHA or other bodies. Collection Facilities that are not in compliance with applicable governmental law cannot be accredited by FACT or JACIE. Non-compliance with Standard C1.2 identified in an accredited program or facility may jeopardize that accreditation.

STANDARD:

C1.3 The Collection Facility, including the 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 prior to being eligible for initial accreditation.

C1.3.1 For apheresis collection facilities, a minimum of ten (10) apheresis collection procedures shall have been performed in the twelve (12) months preceding application for accreditation.

C1.3.2 For bone marrow collection facilities, a minimum of one bone marrow collection procedure shall have been performed in the twelve (12) months preceding application for accreditation.

C1.4 For renewal accreditation of apheresis collection facilities, a minimum of thirty (30) apheresis collection procedures shall have been performed within an accreditation cycle.

C1.5 For renewal accreditation of bone marrow collection facilities, a minimum of three (3) bone marrow collection procedures shall have been performed within an accreditation cycle.

GUIDANCE:

This standard refers specifically to the number of apheresis procedures for cellular therapy products, not the number of patients from whom HPC and / or TC were collected. For marrow collections, the donors may be autologous or allogeneic donors.

Apheresis facilities that are active in the collection of mature 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.

C2 COLLECTION FACILITY

STANDARD:

C2.1 Where required, the Collection Facility shall be registered with the FDA or non-U.S. equivalent for the activities performed.

GUIDANCE:

Any facility that is involved with the recovery, screening, testing, packaging, processing, storage, labeling, or distribution of cellular therapy products in the United States, is required to register with the FDA annually (21 CFR 207, 807, and 1271). This registration requires a listing of the activities in which the Collection Facility engages and a listing of each 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. HPC, Marrow is excluded if it is minimally manipulated, not combined with a drug or a device, and is for homologous use. More information regarding the requirements and process for FDA registration can be found at: http://www.fda.gov/cber/tissue/tisreg.htm. Note that each activity performed by the institution must be registered, regardless of who performs the activity. A Collection Facility that is within a larger institution such as a hospital or medical center may combine its registration with other services related to the same regulations. Activities that may be performed by a collection facility include the apheresis collection procedure screening of donors for infectious disease risk to determine eligibility, and temporary storage of products.

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.

The inspector should look for documentation of FDA registration within the U.S., or documentation of a similar registration that may be required outside of the U.S. A copy of the validated FDA registration document 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. A copy may not be immediately available in the Collection Facility; however, the Director or Medical Director should know who in the institution is responsible for the registration, and where a copy may be obtained. It is not appropriate to request a faxed copy from the FDA during the on-site inspection.

STANDARD:

C2.2 There shall be appropriate designated areas for collection of cellular therapy products, for the product collected, and for storage of supplies and equipment.

C2.2.1 The 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.

C2.2.2 There shall be suitable and confidential space for donor examination and evaluation.

C2.2.3 There shall be a designated area for appropriate preparation and storage of the reagents and equipment needed for the performance of the collection procedure.

C2.2.4 The Collection Facility shall provide adequate lighting, ventilation, plumbing, drainage, and access to sinks and toilets to prevent the introduction, transmission, or spread of communicable disease.

GUIDANCE:
The inspector will tour the Collection Facility during the on-site inspection, including all locations where products are collected, stored, and distributed. The space used for collection and storage of HPC should be well-defined and adequate and there should be designated space for preparation and storage of reagents and equipment.

The inspector should observe the organization, design, location, and amount of space available in the 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 product. At a minimum, there should be ample lighting, a temperature controlled environment, monitored as appropriate, and access to hand-washing and toilet facilities. There should be clearly designated areas for product labeling, and storage that are separate from the collection area. The inspector should ask personnel to demonstrate where each of these activities is typically performed, how a product moves through the Collection Facility, and how products and associated paperwork are segregated if more than one product is present in the facility. Inspectors should note safeguards in place to prevent mislabeling, inappropriate product release, or mix-ups. There should be an approved method of cleaning of the facility and the equipment, and that cleaning should be documented. The physical facility should be orderly and organized according to a defined workflow.

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.

Storage areas for HPC and TC must be designated and controlled to prevent mix-ups and contamination regardless of the duration of the storage. Storage includes temporary holding of a product after collection and prior to transport to a processing facility It is critical that the storage area be, at a minimum, secure and temperature controlled and that the products be appropriately labeled and segregated, particularly for those products that may be held in the collection facility overnight, and transported the following day with a second collection from that donor.

The inspector should also verify that there is appropriate space devoted to donor examination and evaluation. At a minimum, such space should provide for auditory privacy at the time of donor interview and full privacy for examination. It is not acceptable to perform donor interview at the bedside unless privacy is preserved. The inspector can request a mock interview if there is a question of space size and/or location. It is critical that patients' and donors' confidentiality and privacy is protected by all reasonable means.

There is no definition of adequate space. Although there is no national standard for the amount of space necessary to provide a safe environment for PBPC 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. If the space seems to be inadequate, this should be discussed by the inspectors and appropriate suggestions, with recommendations, should be included in the report to the FACT or JACIE Accreditation Committee.

The inspector should investigate what other activities are performed on the equipment and in the space assigned to the PBPC Collection Facility. 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. 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.

STANDARD:

C2.3 There shall be adequate equipment for the procedures performed at the facility.

C2.4 There shall be a process to control storage areas to prevent mix-ups, contamination, and cross contamination of products during quarantine, prior to release or transport to the Processing Facility, and for non-conforming products.

GUIDANCE:

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

C2.5 There shall be a transfusion service providing 24-hour availability of CMV-appropriate and irradiated blood products.

C2.6 There shall be access to an intensive care unit and/or emergency services.

The inspector should visit the blood bank to verify the availability of irradiated, leukoreduced and/or Cytomegalovirus (CMV) seronegative cellular blood products and other blood components on a 24-hour basis.

The Standards aim to protect donor/patient safety in the rare emergency situation. 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, e.g., electrocardiograph, crash cart, code team (in the hospital), or ACLS-trained individuals (free standing facilities). If the only emergency response available to the facility is a community-based emergency service (such as “911”), the inspector should be able to verify that such an option is feasible and provides for a reasonably safe collection. The inspector should request protocols for emergency response, training and competency personnel files, and a contract or a letter of understanding with local emergency services as to the minimal expectations of the transplant program. 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:

C2.7 SAFETY REQUIREMENTS

C2.7.1 The Collection Facility shall be operated in a manner to minimize risks to the health and safety of employees, patients, donors, and visitors.

C2.7.2 Instructions for action in case of exposure to communicable disease or to chemical, biologic, or radiological hazards shall be included in the safety manual.

C2.7.3 Medical waste shall be disposed of in a manner that minimizes any hazard to facility personnel and to the environment, in accordance with applicable governmental laws and regulations.

C2.7.4 The Collection Facility shall be maintained in a clean, sanitary, and orderly manner.

C2.7.5 Gloves shall be worn while handling biological specimens.

GUIDANCE:
This Standard applies to all facilities involved in hematopoietic progenitor cell therapy (Clinical Programs, Collection, and Processing Facilities). Safety training, including universal precautions ("Standard" precautions according to the Center for Disease Control) for handling blood is a requirement of OSHA. The facility policies and procedures, including housekeeping and waste disposal, must document consistency with good biosafety procedures, including adherence to universal precautions and to federal, state, or provincial regulations regarding safety.

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.

Any potentially biohazardous material shall be discarded in a safe manner according to written protocols for the disposal of biohazard waste. Contaminated materials may be discarded by autoclaving, ultra-high temperature incineration, decontamination with hypochlorite solution, and, in some locations, the use of a landfill. Radioactive waste must be discarded using methods approved by appropriate governmental agencies. Also, facilities should post warning signs wherever radioactive materials are in use. Facility personnel responsible for these activities should be identified.

Each facility shall have a safety manual. 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. The facility may keep a condensed or summarized hard copy of the institutional safety manual in the Collection Facility. In this case, there must be written documentation of how the safety manual is kept updated with institutional revisions. Alternatively, 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 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. Safety, infection control, or biohazard waste disposal procedures that are unique to the Collection Facility should be covered in the Collection Facility SOP manual.

If a collection procedure is underway during the day of inspection, the inspector should observe personnel for use of protective clothing and other biosafety precautions. If there is no collection procedure underway, the inspector should ask that a mock procedure be demonstrated. 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. The inspector should examine how products are being handled and discarded (e.g. incinerator, waste field, etc.) and compare his/her observations with the written protocols. Compliance with state, federal, and/or applicable national 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.

C3 PERSONNEL

STANDARD:

C3.1 COLLECTION FACILITY DIRECTOR

C3.1.1 There shall be a Collection Facility Director who is an individual with a medical degree or doctoral degree in a relevant science, qualified by postgraduate training or experience for the scope of activities carried out in the Collection Facility. The Collection Facility Director may also serve as the Collection Facility Medical Director, if appropriately credentialed.

C3.1.2 The Collection Facility Director shall be responsible for all technical procedures, performance of the collection procedure, supervision of staff, and administrative operations of the Collection Facility.

C3.1.3 The Collection Facility Director shall have at least one year experience in the cellular therapy product collection procedure; and shall have performed or supervised at least ten (10) collection procedures of each type (HPC, Apheresis and/or HPC, Marrow) for which the collection facility is requesting accreditation.

C3.1.4 The Collection Facility Director shall participate regularly in educational activities related to cellular therapy product collection and/or transplantation.

C3.2 COLLECTION FACILITY MEDICAL DIRECTOR

C3.2.1 There shall be a Collection Facility Medical Director who is a licensed physician with postgraduate training in cell collection and/or transplantation. The Collection Facility Medical Director may also serve as the Collection Facility Director, if appropriately credentialed.

C3.2.2 The Collection Facility Medical Director or designee shall be directly responsible for the medical care of patients undergoing apheresis or marrow harvesting, including the pre-collection evaluation of the donor at the time of donation and care of any complications resulting from the collection procedure.

C3.2.3 The Collection Facility Medical Director shall have at least one year experience in cellular therapy product collection procedures, and shall have performed or supervised at least ten (10) such collection procedures of each type (HPC, Apheresis and/or HPC, Marrow) for which the Collection Facility is requesting accreditation.

C3.2.4 The Collection Facility Medical Director shall participate regularly in educational activities related to cellular therapy product collection and/or transplantation.

GUIDANCE:

The Collection Facility Director should be an individual with a relevant doctoral degree. A Medical Doctor (M.D.) degree qualifies as a relevant doctoral degree; a non-physician director may hold a doctoral degree in any of the biological sciences. The 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 Quality Management Program, maintenance of all equipment, data analysis, reporting, and compliance of the Collection Facility with these Standards and applicable law.

The Medical Director must be a physician licensed to practice medicine in the state, province or country

in which the Collection Facility is located and have postdoctoral training in fields such as blood and/or marrow collection and/or transplantation. The Medical Director need not be licensed in other jurisdictions in which satellite Collection Facilities are located. To fulfill this standard, the Medical Director must provide a photocopy of his/her current state, provincial, or national license. Since documentation of the M.D. 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 facility 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.

The Medical Director is directly responsible for the medical care of donors and patients undergoing 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 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 Collection Facility Director and Medical Director must have at least one year's experience in the collection procedure and have performed or supervised at least 10 collection procedures of each type for which the Collection Facility is requesting accreditation. 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. Experience can include training as part of a residency or fellowship program, specific training in another facility, and/or on-the-job training. The Collection Facility Director and Medical Director are expected to participate regularly in educational activities related to the field of hematopoietic cell collection and/or transplantation. 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. If documentation of the number of hours of continuing medical education (CME) or continuing professional development (CPD) is provided, the inspector should verify that the hours were in activities relevant to cellular therapy product collection or transplantation.

The Collection Facility Director and Medical Director are required to submit Curriculum Vitas (CV) that demonstrate 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. The Collection Facility Director and Medical Director may have other responsibilities, but s/he or a designee should be available at all times when the Collection Facility could be operational. The Collection Facility Director and Medical Director responsibilities should be specifically documented.

STANDARD:

C3.3 OTHER STAFF

C3.3.1 There shall be adequate numbers of trained support personnel available at the Collection Facility.

C3.4 For Collection Facilities collecting cellular therapy products from pediatric donors, physicians and collection staff shall have documented training and experience in performing these procedures.

GUIDANCE:

The standards require that there be an adequate number of trained personnel available for the collection of progenitor cells relative to the workload. The number of staff available and other responsibilities of the staff will vary from institution to institution, and no specific numbers of staff members are required by the

FACT-JACIE Standards. 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. There should be sufficient staff present to manage in the event of any donor emergency without neglecting ongoing collections. Insufficient staffing may also be indicated by excessive overtime, rapid turnover of personnel, incomplete record keeping, or an increase in adverse events.

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 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. 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. 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 staffs' medical records (e.g., vaccinations and health records). The Collection Facility Director should indicate personnel responsible for specific activities in the Collection Facility and confirm that they are appropriately trained to perform those activities. Additional information related to training and competency is addressed in the Quality Management section of Standards and this Guidance.

C4 QUALITY MANAGEMENT

STANDARD:

C4.1 The Collection Facility shall have a written Quality Management Plan that addresses, at a minimum:

- *C4.1.1 Organizational structure*
- *C4.1.2 Agreements*
- *C4.1.3 Process development and review*
- *C4.1.4 Personnel qualifications, training, and competency*
- *C4.1.5 Outcome analysis*
- *C4.1.6 Audits*
- *C4.1.7 Management of cellular therapy products with positive microbial culture results*
- *C4.1.8 Detection and reporting of errors, accidents, and adverse events*
- *C4.1.9 Record review and document control*
- *C4.1.10 Validation of reagents, equipment, and procedures*
- *C4.1.11 Qualification of facilities, reagents, supplies, and equipment*
- *C4.1.12 Inventory control*
- *C4.1.13 Product tracking*
- *C4.1.14 Process control*

GUIDANCE:

Development of a written comprehensive Quality Management (QM) Program is often the most challenging and time-consuming exercise that the Collection Facility will encounter when preparing for a FACT or JACIE inspection. This edition of the Standards has broadened the scope of requirements of the Quality Plan for the Collection Facility to be more in line 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 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.

There must be a written QM plan that includes all of the elements listed in standards C4.1.1 through C4.1.14. 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 Collection Facility. For example, for some elements the 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 nature of participation by other areas and/or institutions. An integrated Transplant 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. However, it remains the responsibility of the Collection Facility to ensure that all elements of the QM Program required in part C4 are in place and functioning and that documentation of compliance to standards that are not performed by Collection Facility staff is available to the facility.

The written QM plan for the Collection Facility will be provided to the inspector prior to the on-site inspection. The inspector is expected to evaluate implementation of the QM plan at the facility and the understanding of quality management by the staff. The thoroughness and attention to detail of the written QM plan is an indication of how QM is perceived and executed within the program. An incomplete or poorly written QM plan is an indication that QM is not deemed an integral and important component of the program. Under these circumstances, the inspector should pay particular attention to evaluating the QM efforts of the program during the on-site inspection process. The inspector should specifically look for documentation of compliance for QM activities not directly performed by Collection Facility staff.

STANDARD:

C4.2 There shall be a Collection Facility Director who is responsible for the Quality Management Plan as it pertains to the Collection Facility. The performance of this activity may be delegated to a designated individual(s) with appropriate training, knowledge, and expertise.

C4.2.1 The designated individual(s) shall have authority over and responsibility for ensuring that the Quality Management Plan is effectively established and maintained.

C4.2.2 The designated individual(s) shall not have oversight of his/her own work if this person also performs other tasks in the Collection Facility.

C4.2.3 The designated individual(s) shall report on quality management activities, at a minimum, quarterly.

C4.2.4 The designated individual(s) shall provide a report on the performance of the Quality Management Plan, at a minimum, annually to the Collection Facility Director and, if applicable, the Clinical Program Director.

GUIDANCE:

There must be a designated person to oversee the QM Program. The Transplant Program Director is ultimately responsible for performance of the quality plan and monitoring of all program elements, internal or contracted. The Transplant Program Director may delegate responsibility for oversight of designated parts of QM to other persons. Such delegation should be documented, either in the QM Plan or in procedures related to it. For example, the Collection Facility Director or Medical Director frequently

assumes responsibility for the collection aspects of QM as related to the transplant program. The Transplant Director may also be assisted by a Clinical Program Director (for pediatrics or internal medicine), or a Clinical Unit Director, who may have designated responsibilities for review and management of elements of QM such as the review and management of errors, accidents, and adverse events.

The day-to-day tasks of the QM Program may also be delegated to an individual within the program with sufficient expertise. This person 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 Transplant Program; or it could be a member of the transplant team who has additional responsibilities within the program. However, the designated person must have sufficient knowledge and training to facilitate the identification of improvement opportunities by the staff.

The Collection Facility Director, or a properly qualified designee, is responsible for the QM Plan as it pertains to the Collection Facility. A Collection Facility QM Supervisor must be designated. The same person may be responsible for QM of all components of the 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. The identified responsible person should not be directly responsible for review of work solely performed by that person. It may be acceptable 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 programs where there may be only one person responsible for most of the collection activity, the Director, Medical Director, or a person from the laboratory may be designated for review of these activities.

The inspector should ask to see evidence that the outcome of Quality Assessments is communicated to key individuals within all participating entities in the program. Communication is most effectively accomplished by regularly scheduled QM meetings. 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 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.

STANDARD:

C4.3 The Quality Management Plan shall include an organizational chart of key personnel and functions within the Collection Facility.

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

GUIDANCE:

The organizational chart should include the reporting structure for the Collection Facility QM Program. 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. The description of the operation of the quality program should include the mechanisms (meetings), participants, schedule, and documentation. 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 program. The inspector should review any documents that support the described organizational structure. The documentation should include the names and responsibilities of all critical

staff. Lines of responsibility and communications must be clearly defined in a way that is understood by all involved. The organizational chart for the entire program, as well as for the Collection Facility, will be provided to the inspector prior to the on-site inspection. The inspector will verify that the organization and daily function is as described.

STANDARD:

C4.4 The Quality Management Plan shall include policies and procedures for development and implementation of written agreements with third parties whose services impact the cellular therapy product.

GUIDANCE:

The inspector should review the process for establishing agreements or contracts with entities outside of the Collection Facility that participate in 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. Such agreements may include, but are not limited to donor qualification, determination of donor suitability and eligibility, procurement (collection) of the 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.

How such agreements are executed is a function of the type of Collection Facility. For example, stand-alone facilities may execute agreements directly with the service providers (or institutions for which they provide services), whereas agreements involving Collection Facilities in academic institutions may be between the institution and the service provider. In all cases, a process must exist for the development and implementation of such agreements. The 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 Collection Facility (or an entity with which the Collection 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.

STANDARD:

C4.5 The Quality Management Plan shall include methods for process development, approval, validation, implementation, review, revision, and archiving for all critical processes, policies, and procedures.

C4.5.1 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 and preventive action.

GUIDANCE:

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, outcomes analyses, training records, etc. The QM Program needs to identify the documents critical to the Transplant Program 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 receipt into the laboratory, other processes may require multiple documents for its performance. 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 collection facility, the physician, and the collection program 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. Standard C4.5 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.

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 Collection Facility Director prior to implementation. 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. 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. The inspector will look to see how the program controls modifications of documents and whether retrospective review is possible.

The program should develop and prioritize performance measures. These may include, for example, survival, treatment-related mortality, specific complication rates, and other clinical outcomes, as well as adherence to selected policies or procedures. 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. 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 Collection Facility 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. 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.

STANDARD:

C4.6 The Quality Management Plan shall include personnel requirements for each key

position in the Collection Facility. Personnel requirements shall include at a minimum:

C4.6.1 Current job description for all staff

C4.6.2 A system to document the following for each staff member:

C4.6.2.1 Initial qualifications

C4.6.2.2 Orientation

C4.6.2.3 Initial training

C4.6.2.4 Competency for each function performed

C4.6.2.5 Continued competency at least annually

C4.6.2.6 Provisions for continuing education, training, and retraining

C4.6.3 A description of minimal trainer qualifications and a uniform plan for staff training.

GUIDANCE:
Personnel requirements are to be included in the Collection Facility QM plan and should ensure that each position has specified job duties and responsibilities. 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.

Organization-specific issues are generally covered by orientation programs, but this should be confirmed by the inspector. Legal and regulatory context can be demonstrated by including training related to GTP, GMP, and FACT-JACIE Standards.

The inspector should review procedures or policies describing the elements of staff training and continued competency as described in standards C4.6.2.1 through C4.6.2.6. 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 competency and annual continued competency may be assessed by observation, the use of written tests, successful completion of proficiency surveys, review of collection procedure end-points, or other ways as determined by the Collection Facility. Procedures for personnel training and competency assessment must be defined by an SOP (See C5.1.15). 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 training plan SOP should also define the minimal qualifications of any designated trainers.

STANDARD:
C4.7 The Quality Management Plan shall include a process for documentation and review of outcome analysis and product efficacy, as appropriate, including at least:

C4.7.1 For HPC products, a process for documentation and review of time to engraftment following product administration.

GUIDANCE:
Outcome analysis involves the collection, evaluation, and distribution of patient outcome data, including engraftment in the case of HPC products. Acceptable criteria for each product should be developed by the Collection Facility in conjunction with the clinical team and this process defined by an SOP (See C5.1.20). 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 Collection Facility personnel should evaluate all aspects of the collection procedure related to any unexpected outcome, including delayed or failed engraftment. This evaluation should be documented, and, if indicated, the Collection Facility should initiate corrective action. The inspector should confirm documentation of all activities from definition of expected outcome to process improvement, when indicated.

Timely engraftment of the HPC product in a recipient following a myeloablative regimen is directly related to the quality of that HPC product. Therefore, the Collection Facility personnel must be aware of the time to neutrophil and platelet engraftment for all patients for whom they have supplied products. This information can be obtained and analyzed directly by the Collection Facility or presented by another section of the Transplant Program at a common quality management meeting where Collection Facility personnel are in attendance. It is not required for each section of the transplant program to independently analyze engraftment. The inspector should ask to see the engraftment data and/or minutes of meetings, including the personnel in attendance, where engraftment data are presented.

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 Collection Facility may also consider number of collections per patient, cell yield per collection, or duration of each collection in its 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 Collection Facility. However, it is the responsibility of the Collection Facility to have (or provide) access to this data to both the Clinical Program and the Laboratory.

If a Collection Facility provides products to one or more Clinical Programs, it is the responsibility of the Collection Facility to solicit engraftment data from each program.

STANDARD:
C4.8 The Quality Management Plan shall include a process and timetable for conducting independent quality audits of the Collection Facility's activities to verify compliance with elements of the Quality Management Program.

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

C4.8.2 Audit results shall be reviewed, reported, and documented at a minimum, on a quarterly basis.

C4.8.3 The results of audits shall be used to recognize problems, detect trends, and identify improvement opportunities.

C4.8.4 Audits shall include, at a minimum, documentation of proper donor eligibility and determination.

GUIDANCE:
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. 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 head of the Collection Facility Quality Program should identify areas to be audited and audit frequency. Standard C4.8.2 indicates that audits should be performed minimally on a quarterly basis. This does not mean that the same audit is performed quarterly, rather the audit process should be performed throughout the year with quarterly review and 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 Collection Facility conducts the audit, such individuals may not have the needed expertise. The process by which the Collection Facility performs audits must be defined by an SOP (See D5.1.21).

Audits should be performed of activities where failure may result in a compromised 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. Examples of audits in the 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
- Collection equipment used identified for each collection
- Collection efficiency
- Complete records of donor eligibility available for each collection
- Complete documentation that reagents and supplies were used prior to expiration
- Cleaning and sanitation performed according to SOP and documented

There should be evidence that audit reports are shared with the Collection Facility staff, the Collection Facility Director and Medical Director as appropriate, the Program Director, Laboratory, and others with potential interest. The inspector should review the audit process and example audits to determine 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.

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.

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.).

STANDARD:

C4.9 The Quality Management Plan shall include policies and procedures on the management of cellular therapy products with positive microbial culture results that address at least:

C4.9.1 Documentation and product labeling.

C4.9.2 Release of the product from the distribution facility, including identification of authorized individuals and criteria for product release.

C4.9.3 Investigation of cause.

C4.9.4 Notification of transplant physician, Collection Facility and/or Cell Processing Facility, as applicable.

C4.9.5 Notification of the recipient prior to infusion.

C4.9.6 Recipient follow-up and outcome analysis.

C4.9.7 Follow-up of the donor, if relevant.

C4.9.8 Reporting to regulatory agencies, if appropriate

GUIDANCE:

The Transplant Program must develop an integrated approach to the management of cellular therapy products with positive microbial culture results that are identified either before or after the products have been infused. Policies and procedures are required in all three areas of the transplant program – clinical, collection, and laboratory. These Standards list the topics that must be addressed in policies, but do not dictate a single policy 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.

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 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. In the U.S., regulations for 351 and 361 products should be followed and the program should have policies that cover responsibility for reporting. Labeling requirements may be defined by the institution and should include requirements for the use of a biohazard label and warning statements. 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 other cases, a positive result may only become available after the product has been infused. The laboratory is usually the first facility to be notified of a positive culture result. There should be timely notification of the Collection Facility, which should in turn investigate all records related to that collection to determine if anything in the collection process could have contributed to the positive culture result.

The 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.

STANDARD:

C4.10 The Quality Management Plan shall include a system for detecting, evaluating, documenting, and reporting errors, accidents, suspected adverse events, biological product deviations, and complaints.

C4.10.1 Documentation of each adverse event that occurs in the Collection Facility shall be reviewed by the Collection Facility Director and/or Medical Director, as appropriate.

C4.10.2 Adverse events in the Collection Facility shall be documented in a manner that complies with institutional requirements and applicable governmental laws and regulations.

C4.10.3 Deviations from Standard Operating Procedures shall be documented.

C4.10.3.1 Planned deviations shall be pre-approved by the Collection Facility Director or designee.

C4.10.3.2 Unplanned deviations and associated corrective actions shall be reviewed by the Collection Facility Director or designee.

C4.10.4 Corrective actions shall be implemented, as appropriate. These shall include both short-term action to address the immediate problem and long-term action to prevent the problem's recurrence.

C4.10.5 Effectiveness of corrective actions shall be verified.

C4.10.6 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.

C4.10.7 When applicable, the event shall be reported to appropriate regulatory agencies.

C4.10.8 There shall be policies and procedures to document and follow-up customer-reported product failures, concerns, or complaints.

GUIDANCE:

There must be a mechanism 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 Collection Facility should define errors, accidents, deviations, adverse reactions, and complaints in an SOP (See C5.1.18 and C5.1.19) along with when and how each is reported.

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.

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.

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.

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 Collection Facility Director, Collection Facility Medical Director, and potentially the Clinical Program Director. The inspector should ask to see SOPs that describe how adverse reactions are detected, investigated, and reported, files of adverse reactions, and evidence that adverse reactions are reviewed by the Collection Facility Director and reported as appropriate to the Clinical Program Director, the transmitting facility, and appropriate governmental agencies.

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 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. EUDs 2006/17/EC and 2006/86/EC include equivalent requirements for non-conforming products. How the Collection Facility manages biological product deviations in general should be addressed by the QM Program or by other policies or procedures and must be defined in an SOP (See C5.1.11). The most common biological product deviations encountered involve products with a positive microbial culture (as described in the guidance for Standard C4.9) or products from ineligible donors. Specific issues regarding products from ineligible donors are addressed in the guidance for Standard C6.2.

If there is a complaint of 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 re-occurrence as defined by an SOP (See C5.1.19). 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.

STANDARD:

C4.11 The Quality Management Plan shall include a mechanism for document control and for

the regular review of records relating to cell collection and transportation. The document control system shall include at a minimum the following elements:

C4.11.1 Definition and current listing of all critical documents that must adhere to the document control system requirements.

C4.11.2 Assignment of a numeric or alphanumeric identifier to each document regulated within the system.

C4.11.3 A procedure for document approval, including the approval date, signature of approving individual(s), and the effective date.

C4.11.4 A system to ensure that controlled documents cannot undergo accidental or unauthorized modification.

C4.11.5 A system for documentation of training associated with each procedure and its revisions.

C4.11.6 A system for document change control that includes a description of the change, the signature of approving individual(s), approval date, and effective date.

C4.11.7 A system for the retraction of obsolete documents to prevent unintended use.

C4.11.7.1 Obsolete documents shall be archived for a minimum of ten (10) years.

C4.11.8 A system for record creation, assembly, storage, archival, and retrieval.

GUIDANCE:
This standard primarily addresses the need for a comprehensive document control system that covers all of the critical documents used by the Collection Facility. Documents that fall under this system should be listed and minimally include:

- Policies
- Procedures
- Labels
- Worksheets and checklists
- Forms

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 Collection Facility Director should determine which documents fall under this system.

The inspector should confirm that a written change control policy exists and is effective to prevent unintended changes to processes, policies, or SOPs. The change control policy 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. The inspector should confirm that the change control policy meets these minimal criteria and that the policy is followed.

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.

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

STANDARD:

C4.12 The Quality Management Plan shall include a process for product tracking that allow tracking from the donor to the recipient or final distribution and from the recipient, or final disposition, to the donor.

GUIDANCE:

One of the most important paper trails in the Collection Facility allows for tracking 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, 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 (C5.1.12).

The inspector should review examples of specific products at the 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.

STANDARD:

C4.13 The Quality Management Plan shall include a mechanism to ensure continuous operations in the event that the electronic record system ceases to function, including a plan for data backup, and a mechanism to ensure compliance with applicable laws.

GUIDANCE:

The 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.

The inspector should review policies and forms to be used in case the electronic record keeping system is unavailable. Specifically in the Collection Facility, this should include a mechanism to ensure and document donor eligibility and suitability 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. The inspector should determine if products can be produced to the same standard of quality even when the electronic records are not available.

STANDARD:

C4.14 The Quality Management Plan shall include a process for validation and verification of critical reagents, equipment, and procedures.

C4.14.1 There shall be documentation of review and acceptance of validation studies by the appropriate individual from Quality Management.

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.

GUIDANCE:

Validation is confirmation by examination and provision of objective evidence that specific requirements can be consistently fulfilled. Validations can be performed prospectively, concurrently or retrospectively. Validations should be performed on processes, equipment, reagent, and supplies. In the Collection Facility, the following should be validated at a minimum:

1. The apheresis device. Each type of apheresis machine should be validated for the 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 validation of processes.
2. The collection procedure. 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); procedural variables (e.g., machine program chosen, blood volume processed, duration of collection). The validation study should demonstrate that the procedure reproducibly results in a product that is sterile, and is of a predetermined volume and nucleated cell content.
3. 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 included all of the required elements as listed on the label table (FACT-JACIE Standards, Appendix 1). Validation of the labeling process would demonstrate completeness and correctness of each data point, accuracy of data as shown by traceability and trackability of the product from donor to recipient, or final disposition.
3. Reagents. Most Collection Facility reagents 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 equipment or process achieves the purpose for which it is intended. The validation plan should state specifically the tests to be performed, the number of samples to be tested, and the range of acceptable results. 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 inspector should review a sampling of validation studies of the facility, processes, reagents and equipment. The inspector should note poorly designed or inadequately performed validation studies during the review process. The validation studies must include documented review by the QM Supervisor and/or other appropriate individuals from Quality Management.

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

Collection Facility or the manufacturer. In the case of manufacturer validation, the certificate of analysis should be available in the facility.

It is acceptable, but not required, for the Collection Facility to utilize validation plans, formats, and personnel from the Processing Laboratory to perform validation studies, or to contract these validation services to a contract vendor. In either case, the validations must be performed on the equipment in place in the Collection Facility for the specific cellular therapy procedures performed at that facility.

STANDARD:

C4.15 The Quality Management Plan shall include a process for qualification of critical reagents, equipment, procedures and facilities.

C4.15.1 Critical procedures shall include at least the following: collection procedures, labeling, storage conditions, and transportation.

C4.15.2 Equipment, supplies, and reagents used to collect cellular therapy products shall be used in a manner that prevents product mix-ups, contamination and cross-contamination, and that does not compromise cellular product function and integrity.

C4.15.3 Supplies and reagents used in collection of cellular therapy products shall be stored at the appropriate temperature in a secure, sanitary, and orderly manner.

C4.15.4 All supplies and reagents coming into contact with cellular therapy products during collection, storage, or transportation shall be sterile and shall be of appropriate grade for the intended use.

C4.15.4.1 Reagents that are not of the appropriate grade shall undergo qualification for the intended use.

C4.15.4.2 Non-disposable supplies or instruments shall be cleaned and sterilized using a procedure validated to remove infectious agents.

C4.15.5 Supplies and reagents should be used in a manner consistent with instructions provided by the manufacturer.

C4.15.6 There shall be a process to prevent the use of expired reagents, supplies, and obsolete labels.

GUIDANCE:

Quality can be maintained only if there is control over critical supplies, reagents, equipment, procedures, and the facility itself. Qualification is defined in these Standards as “The establishment of confidence that processes, equipment, and reagents function consistently within established limits.” Here the Standards define the critical procedures that must be qualified, even after validation, to include procedures for the collection, testing, cryopreservation, storage, and transport of cellular therapy products.

Procedure qualification can be performed by determining expected outcomes at critical steps and monitoring that these outcomes are achieved, by establishing the minimal acceptance criteria for the reagents, materials and supplies used in collection, and by maintenance and calibration schedules for equipment used to ensure their proper performance as defined by an SOP (See C5.1.17).

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. The inspector should observe the 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. Questions may be asked to determine: Are products from different patients stored in the Collection Facility at the same time? Are products labeled at the donor's side prior to disconnecting from the apheresis line to avoid misidentification? Are reagents identified as dedicated to a single collection procedure? Is there a record of the lot numbers and expiration dates for all reagents used in collection? Is the specific apheresis machine used in each collection identified? How is cleaning and disinfection performed between collection procedures?

Once received, supplies and reagents used for collection must be stored in a manner that preserves their function and sterility. The inspector should observe storage areas and confirm that supplies and reagents are stored under the conditions specified by the manufacturer. For items requiring storage at a specified temperature range, the temperature of the storage area must be monitored and documented. 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. This 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.

Whenever possible, supplies and reagents that come into contact with cellular therapy products should be clinical grade, and must be free of microbial contamination. If a supply or reagent is not clinical grade (i.e. labeled for research only), it should be of the highest grade (or purity) available and the Collection Facility must have demonstrated that the supply or reagent functions consistently within the established limits. The inspector should review how such reagents were qualified. Use of supplies and reagents according to manufacturer's instructions is recommended, when possible and appropriate.

For some specialized collection procedures, equipment or instruments that come into contact with the product may require cleaning and sterilization between uses. When this is the case, the Collection Facility must verify that the cleaning and sterilization methods used remove infectious agents. The inspector should review the records of this verification process.

There should be a mechanism to monitor the flow of supplies and reagents within the facility to prevent the use of outdated supplies and reagents. 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. 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. 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.

STANDARD:

C4.15.7 There shall be a system to uniquely identify and track all critical equipment used in the collection of cellular therapy products.

C4.15.8 Equipment used in the collection, testing, storage, or transportation of cellular therapy products shall be maintained in a clean and orderly manner and located to facilitate cleaning, calibration, and maintenance.

C4.15.9 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.

C4.15.10 Equipment shall conform to existing legislation/regulations, where applicable.

GUIDANCE:
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 collection. Therefore, equipment used in collection that might affect product quality must be identified and tracked. For this purpose, standard C4.15.7 requires that there be a system by which the critical equipment can be uniquely identified. 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", is less desirable since over the course of time more than one centrifuge might fit that description. Additionally, equipment should be identified even if there is only one of a specific piece of equipment. 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.

In parallel to the standard for supplies and reagents, it is also important that the system in use allows for the identification of all cell therapy products processed using a given piece of critical equipment.

Equipment used for collection or product testing must be maintained, calibrated, cleaned, and, if applicable, sterilized. Equipment SOPs must also describe how the equipment is operated or refer to relevant operations manuals that are available within the Collection Facility. 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. It is recommended that recent records of regularly scheduled maintenance and quality control be readily available for each piece of equipment. Tags or stickers should be visible on the equipment indicating that QC parameters have been met, the date QC testing was performed and when it 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. 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 C5.1.17 and C5.1.19). This should include an investigation of potential adverse effects on manufactured products using the equipment tracking system. Note that if critical equipment used in collection is located outside of the Collection Facility, such as sterilization equipment, it is the facility's responsibility to 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 C5.1.23). This is important to prevent microbial contamination of products, as well as to prevent transmission of infectious disease and cross-contamination. The inspector should confirm by visual inspection that equipment can be easily accessed for cleaning and maintenance.

EUD 2006/17/EC Annex IV 1.3.10 specifies that where possible, equipment that is compliant with the CE Marking Directive are 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:

C4.15.11 Critical 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.

C4.15.12 There shall be documentation of facility cleaning and sanitation, environmental conditions, and inspection of environmental control systems to ensure adequate conditions for proper operations.

C4.15.12.1 Records of all cleaning and sanitation activities performed to prevent product contamination shall be maintained ten (10) years after their creation.

GUIDANCE:

The Collection Facility must identify the facility parameters that should be controlled and monitored based on their potential effect on product quality. The typical HPC Collection Facility operates with unclassified air, but may require control of temperature and humidity at a minimum. Environmental monitors for measures of air quality, such as particle counts and/or microbial colony counts may be recommended, but in the US, no specific air quality classification is required where collections are performed using closed systems as in apheresis.

EU guidelines are more specific, requiring a background environment appropriate for the collection of the cellular therapy product, but minimally equivalent to GMP Grade D in terms of particles and microbial counts. See the European Commission Enterprise Directorate "EC Guide to Good Manufacturing Practice Revision to Annex 1", Brussels, May 30, 2003, for additional information. This guide may be found at: http://www.hpci.ch/files/documents/guidelines/hh_gl_gmp.pdf.

Contaminants in the 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). There must be ongoing monitoring of any parameters that have been determined to be critical and these should be defined by an SOP (See C5.1.22) and compliance documented through quality records.

Collection Facility cleaning and sanitation must be performed on a regular basis in order to prevent contamination and cross-contamination of products. The methods used must be specified by an SOP (See C5.1.23). 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 ceiling also fall under this standard. The Collection Facility, together with the cleaning services vendor, must establish SOPs for this activity. Facility cleaning must be documented and the records maintained for 10 years.

STANDARD:

C4.16 The Quality Management Plan shall include a process for inventory control that encompasses reagents, supplies, and labels.

C4.16.1 There shall be a system to uniquely identify and track all critical reagents, supplies, and labels used in the collection of cellular therapy products.

C4.16.2 Each supply and reagent used to collect cellular therapy products shall be examined visually for damage or evidence of contamination upon receipt.

GUIDANCE:
The inspector should confirm that there is a process in place to determine acceptability of all critical materials (reagents, supplies, labels, products, and product samples) before they are accepted into inventory and made available for use. This process must be described in an SOP (See C5.1.16). Critical materials must be defined by the Collection Facility and tracked. 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.

Each product must be assigned a unique alphanumeric identifier that is part of the inventory control system. Generally, the product inventory and reagent and supply inventory are separately managed. Product samples 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 inspector should review the inventory control process and documentation of supply and reagent examinations at receipt. The system in use may utilize an electronic system or a log book to enter all incoming supplies and materials. The system must include documentation that materials under the inventory control system meet predefined facility requirements.

STANDARD:
C4.17 The Quality Management Plan shall include a process for controlling and monitoring the collection of products to ensure products meet predetermined release specifications.

C4.17.1 The Collection Facility Director shall define processes for assessing 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 processed.

C4.17.2 Communicable disease testing required by these Standards shall be performed using FDA approved tests in an FDA registered laboratory or non-U.S. equivalent that is accredited or licensed in accordance with applicable governmental regulations.

C4.17.3 Other tests required by these Standards, not performed by the Collection Facility, shall be performed by a laboratory certified by CMS, CLIA, or non-U.S. equivalent.

GUIDANCE:
The establishment of process control is a primary objective of the Collection Facility QM Program. 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. SOPs are required that describe each collection procedure and its associated process control (See C5.1.6).

The Collection Facility Director is responsible for defining release criteria for products distributed by the Collection Facility, identifying the tests to be performed, and testing intervals during collection. The release criteria may differ depending on whether the products are released to a processing facility for further manufacturing or directly to a clinical service for 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. Certain tests on the product or the donor are required to be performed by these Standards, including:

- Communicable disease testing
- HLA typing (allogeneic donors only)
- ABO group and Rh type at collection (product or donor sample)
- Microbial testing after collection (product may be sampled by collection facility or processing laboratory

The results of this testing or other testing designated by the Collection Facility Director, may not always be required for release of the product from the Collection Facility, although samples should have been obtained prior to release unless otherwise specified in SOPs. The inspector should review collection records to determine if all required testing was performed within the required time frame, and if the results are recorded. Documentation that the 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. Additional release criteria that may be pertinent to a product being released to a processing laboratory include the following: product is sealed completely without evidence of leakage, product labeling is complete and correct according to expected data, product has been stored appropriately, expected product and/or donor samples are labeled and available to accompany the product, and donor eligibility determination documentation is available.

Some of the specified testing may be performed by an external laboratory. Communicable disease testing is specifically required by cGTP regulations to be performed using test kits approved for donor screening by the FDA in a CLIA-accredited or FDA-registered laboratory or non-U.S. equivalent laboratory that is accredited or licensed according to local governmental regulations. Since communicable disease testing is usually facilitated by the Clinical Program or Collection Facility prior to collection, the Collection Facility must have a system in place whereby these results are available to the Collection Facility at the time of collection. Communicable disease test results, and verification that testing was in compliance with the requirements of standard C4.17.2, including the name and address of the laboratory performing the testing, must be available for review by the inspector. Other testing not performed by the Collection Facility must be performed by a laboratory certified by CMS, CLIA, or non-U.S equivalent. Such laboratories must have valid and current licenses and/or accreditation. At a minimum, the ASHI or EFI certification of the relevant laboratory performing histocompatibility testing, will have been sent to the inspector in advance. These documents do not necessarily have to be available on-site in the Collection Facility, but documentation that they exist and are currently valid must be reviewed by the inspector. This can take the form of certification and accreditation information that is documented on test result reports.

C5 POLICIES AND PROCEDURES

STANDARD:

C5.1 The Collection Facility shall have documented policies and procedures addressing all appropriate aspects of operations and management including at a minimum:

C5.1.1 Donor and recipient confidentiality

C5.1.2 Donor treatment

C5.1.3 Donor screening

C5.1.4 Donor consent

C5.1.5 Management of pediatric donors, if applicable

C5.1.6 Product collection

C5.1.7 Labeling (including associated forms and samples)

C5.1.8 Expiration dates

C5.1.9 Storage

C5.1.10 Release and exceptional release

C5.1.11 Biological product deviations

C5.1.12 Product tracking

C5.1.13 Transportation

C5.1.14 Quality management and improvement

C5.1.15 Personnel training and competency assessment

C5.1.16 Reagent and supply management

C5.1.17 Equipment maintenance, monitoring, and corrective actions in the event of failure

C5.1.18 Errors, accidents, adverse events, and complaints

C5.1.19 Corrective actions

C5.1.20 Outcome analysis

C5.1.21 Audits

C5.1.22 Facility management and monitoring

C5.1.23 Cleaning and sanitation

C5.1.24 Disposal of medical and biohazard waste

C5.1.25 Emergency and safety

C5.1.26 Disaster plan

GUIDANCE:
The standard requires that each Collection Facility have written policies and procedures that comprehensively address all important aspects of the Collection Facility. The Collection 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. When multiple topics are covered by a single SOP, it will aid the inspection process if the Collection Facility prepares a crosswalk between the list of required procedures in standards C5.1 and the facility's own procedure manual. The items listed in Standard C5.1 include the minimum requirements; a Collection Facility may exceed these requirements, but not omit any of these.

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 Standard C5.2 and C5.3. The policies and procedures can be generated within the Collection Facility or in collaboration with other entities within the institutional infrastructure. This applies most often to SOPs addressing safety, infection control, biohazard disposal, radiation safety, and the emergency response to disasters. In cases where general institutional policies and procedures are inadequate to meet standards or where there are issues that are specific to the Collection Facility, the Collection Facility must develop its own policies and procedures to supplement those of the institution (See C5.1.24 – C5.1.26). In situations where institutional policies and procedures are utilized, there must be a defined mechanism for initial approval and annual review and approval of revisions by the Collection Facility.

The written copy or electronic version (with provision of hardcopy as necessary) of the Collection Facility'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 procedure manual must be identical to the source document and must not be used to alter, modify, extend, delete or otherwise edit any Standard Operating Procedure. 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 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.

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

STANDARD:

C5.2 The Collection Facility shall maintain a detailed Standard Operating Procedures Manual. The Standard Operating Procedures Manual shall include:

C5.2.1 A procedure for preparation, approval, implementation, review, and revision of all procedures.

C5.2.2 A standardized format for procedures, including worksheets, reports, and forms.

C5.2.3 A system of numbering and/or titling of individual procedures, policies, worksheets, and forms.

GUIDANCE:

The SOP manual must have a Standard Operating Procedure outlining the method by which the Collection Facility creates, approves, implements, reviews, and updates its SOPs (the "SOP for SOPs"). 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 Collection Facility 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. 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 "SOP for SOPs" adheres to the requirements for all controlled documents as specified in standard C4.11. 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 facility's standard SOP format.

STANDARD:

C5.3 Procedures shall be sufficiently detailed and unambiguous to allow qualified technical staff to follow and complete the procedures successfully. Each individual procedure requires:

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, including diagrams and tables as needed.

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.

C5.3.7 Documented approval of each procedure and procedural modification by the Collection Facility Director or designated physician prior to implementation and annually thereafter.

C5.3.8 Copies of current versions of orders, worksheets, reports, labels, and forms, where applicable.

GUIDANCE:

This Standard defines the minimum elements required in each SOP. 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 somewhere.

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 CLSI Website. The CLSI format is not required. The facility may use the format of its choice, as long as all listed elements are present. Some 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) or from the Canadian Standards Association website (www.csa-international.org).

Copies of 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 may be prudent to attach one or more completed forms to illustrate possible real life scenarios. Although not required by FACT-JACIE 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.

The Collection Facility should establish a range of acceptable results, when appropriate, for each procedure. Examples include nucleated cell recovery, hematocrit, sterility, plasma volume, etc. The range for a given parameter can be determined within the Collection Facility by evaluating data from its own products. Determination of a mean ± 1 or 2 standard deviations defines an acceptable range.

FACT-JACIE Standards require documented annual review of each procedure by the Collection Facility Director or by the Medical Director 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 Collection Facility Medical Director. It is important that the documentation of annual review 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. 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 the Standard Operating Procedures Manual shall be readily available to the facility staff at all times.

GUIDANCE:

The written copy or electronic version of the SOPs should be readily identifiable to the inspector. The inspector should expect to see the SOP manual or electronic access to SOPs in all performance areas of the Collection Facility. 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.

STANDARD:

C5.5 All personnel in the facility shall follow the Standard Operating Procedures.

C5.6 New and revised policies and procedures shall be reviewed by the staff prior to implementation. This review and associated training shall be documented.

GUIDANCE:

Personnel are required to adhere to the approved SOPs in their manual. Although only annual review is required, when conditions require that a procedure or practice be modified, SOP review and revision must occur in a timely fashion. Documentation that staff have reviewed new and revised procedures and received appropriate training before the procedures are implemented should be reviewed by the inspector. 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 implementation. Training guides specific to each procedure and to any major revision also facilitate documentation of appropriate training of staff.

STANDARD:

C5.7 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.

C5.8 All Standard Operating Procedures shall comply with these Standards and all applicable governmental regulations.

GUIDANCE:
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. The inspector should review the SOP archival system, including local requirements.

While the Collection Facility is expected to adhere to their own operating procedures, those procedures must be in compliance with these Standards and with applicable governmental regulations. A more stringent local standard is acceptable, but not one that contradicts FACT or governmental requirements.

STANDARD:
C5.9 There shall be a process to address age specific issues in the Standard Operating Procedures as appropriate.

GUIDANCE:
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 ever 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. 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 Collection Facility SOP Manuals.
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, and consideration should be given to providing the opportunity for younger donors to sign “assent” to donate.

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.

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.

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.

C6 DONOR SELECTION, EVALUATION, AND MANAGEMENT

STANDARD:

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

C6.2 There shall be donor evaluation procedures in place to protect the safety of the cellular product donor.

C6.2.1 The donor shall be evaluated for potential risks of the collection procedure, including:

C6.2.1.1 Possible need for central venous access and/or mobilization therapy for collection of peripheral blood cells.

C6.2.1.2 Anesthesia for collection of marrow.

C6.2.2 The risk of donation and informed consent shall be documented.

C6.2.3 The use of a donor who does not meet the Clinical Program donor safety criteria shall require documentation of the rationale for his/her selection by the transplant physician.

C6.2.4 Issues of donor health that pertain to the safety of the collection procedure shall be communicated in writing to the Collection Facility staff.

GUIDANCE:

Standards in Section C6 mirror those in B6, reflecting the fact that these responsibilities are usually the primary responsibility of the clinical program staff. Collection Facility staff are usually not responsible for donor selection. Program policies and SOPs must clearly define responsibility for all aspects of donor selection, evaluation, eligibility and suitability determination, and management.

Sections C6.1 through C6.7 apply to both allogeneic and autologous donors. They 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 Section C6.8 to ensure appropriate histocompatibility matching and to protect the recipient from the risks of transmissible disease.

These standards cover the requirements for donor identification, evaluation, selection, and management. The transplant 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. For donors of cellular and tissue-based products, the Food and Drug Administration, or non-U.S. equivalent 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 xenotransplantation, and 3) tests negative or non-reactive for relevant communicable disease agents within the specified time frame for the product. In addition, this Standard requires that the transplant program identify the institutional criteria for donor medical suitability and donor selection. 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.

These standards also require that if chosen donors are ineligible according to FDA regulation 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 by the transplant physician of urgent medical need for the 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 other cellular products. The product should be accompanied by summary of records 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 biohazard legend for cellular 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 the FACT-JACIE Standards Appendix 1.

The inspector should verify that policies and SOPs for donor selection 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.

STANDARD:

C6.3 There shall be donor evaluation procedures in place to protect the recipient from the risk of disease transmission from the donor.

C6.3.1 There shall be procedures for all steps in screening, testing, and determining donor eligibility, and for all regulatory requirements related to cellular therapy donors.

C6.3.2 Within thirty (30) days prior to collection, all HPC donors shall be tested for evidence of clinically relevant infection by the following communicable disease agents:

C6.3.2.1 Human immunodeficiency virus, type 1

C6.3.2.2 Human immunodeficiency virus, type 2

C6.3.2.3 Hepatitis B virus

C6.3.2.4 Hepatitis C virus

C6.3.2.5 Human T-cell lymphotropic virus I (per governmental regulations)

C6.3.2.6 Human T-cell lymphotropic virus II (per governmental regulations)

C6.3.2.7 Treponema pallidum (syphilis)

C6.3.3 Additional tests shall be performed as required to assess the possibility of transmission of other infectious or non-infectious diseases.

C6.3.4 For viable, lymphocyte rich cells, including therapeutic cells, each donor shall be tested for communicable disease agents listed in section B6.3.2 within seven (7) days prior to or after collection, or in accordance with applicable governmental regulations.

C6.4 Any abnormal findings shall be reported to the prospective donor with documentation in the donor record of recommendations made for follow-up care.

GUIDANCE:
Standards included under C6.3 define the minimal evaluation for infectious agents. This applies to autologous donors as well as allogeneic donors. Assessment of all donors is required to minimize the risk of transmitting infection to the recipients as well as to prevent risk of contamination of staff or cross-contamination of other HPC during collection or processing /storage. The FDA regulation also specifies that the donor sample for infectious disease testing must be obtained within 30 days of donation for peripheral blood stem/progenitor cells, and within 7 days of donation for other leukocyte rich cellular products. The EU regulations adopt the same requirements for donor lymphocytes (DLI) as for HPC, i.e. testing for both HPC and lymphocyte donors must be within 30 days prior to donation. Testing must occur in accordance with written SOPs and using appropriate FDA-licensed, approved, or cleared donor screening tests in accordance with the manufacturer's instructions, or non-U.S. equivalent. The results of donor eligibility determination must be recorded.

These standards details minimal laboratory testing. All laboratory tests must be performed by an accredited laboratory as is relevant for the tests (e.g., CLIA, CAP, ASHI, ABBB, JCAHO, HCFA, etc.). 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 7 days prior to collection of other leukocyte-rich cellular products, or as required by applicable regulations.

The inspector should verify that 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. The rationale and informed consent from the donor and recipient should be documented for donors with positive results. The inspector must verify that the donor eligibility determination is recorded.

Other communicable disease tests should be added to the donor evaluation as they become available and recommended to increase the product safety. According to the FDA, there are other relevant communicable diseases besides those specifically listed in the regulations. FDA intends to notify the transplant industry through published guidance from time to time of those additional relevant communicable diseases. 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 either to the recipient or to the staff handling the product because the disease or disease agent:
  - It is transmissible through HCT/P
  - It is sufficiently prevalent as to effect the potential donor population
- There could be fatal or life-threatening consequences as a result of transmission
- There have been developed effective screening mechanisms and/or an approved screening test for donor specimens.

Relevant communicable diseases not specifically listed in the regulation as of August 2007 are:

- West Nile Virus (screening and testing available)
- Sepsis (screening available)
- Vaccinia (screening available)

See FDA Guidance Document ("Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Product [HCT/Ps], 2007) at www.fda.gov/cber/guidelines.htm for additional information.

Testing for West Nile Virus is not currently mandated by the 3rd edition of the FACT-JACIE Standards. However, Standards do require testing for anything determined by regulatory authorities to be relevant communicable disease. 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. Due to the immunocompromised status of HPC recipients, it may be agreed that it is beneficial to perform West Nile Virus testing of allogeneic and autologous donors, at least in regions of the world where WNV has been reported. This would include the U.S. 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. In the event that West Nile Virus testing is performed, the method of testing, the facility performing the testing, interpretation of test results, and actions taken, based on test results, should be clearly outlined in written SOPs.
Abnormal findings in a donor, including but not limited to the testing results, may have important implications for the donor, 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. These actions should be documented in the donor's medical record. The inspector should verify that this documentation is present when indicated. 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 programs.

STANDARD:

C6.5 All donors shall be tested for ABO group and Rh type.

C6.5.1 Allogeneic donors shall be tested for ABO group and Rh type on each day of collection.

C6.5.2 Autologous donors shall be tested for ABO group and Rh type at least on the first day of collection.

C6.6 A pregnancy assessment shall be performed for all female donors of childbearing potential within seven (7) days prior to initiation of recipient's conditioning regimen or of donor starting mobilization regimen.

GUIDANCE:

The donor and recipient's ABO group and Rh type should be determined and documented prior to the collection of HPC from marrow or peripheral blood. There should be documentation in the medical record of these results prior to initiating the collection process. The testing and documentation should occur according to written SOPs. Although identity for ABO and Rh is not essential for donor selection in allogeneic transplantation, this information may be useful if more than one potential donor is available.

SOPs to manage ABO and Rh incompatibility between the donor and recipient should be established. These SOPs may exist primarily in the clinical program or the laboratory; however, some aspects of management may also be important in the Collection Facility. For example, there may be procedures to add or reduce the amount of autologous plasma at the time of collection based on ABO compatibility with the recipient. Specific collection procedures are not required.

In addition, ABO group and Rh testing is required on the product or on a sample from the donor at the time of each collection from an allogeneic donor. Whenever there are past records available, the current result should be compared to previous results, and any discrepancies resolved before proceeding with the processing or infusion of the product. This is in part a verification of donor identity. Additionally, it is inappropriate to label a product with historical results of ABO/Rh. If there is to be a label on the product with this information, the data must be derived from a current sample.

Pregnancy assessment is required since the donation of HPC from marrow or peripheral blood, growth factor administration, and/or anesthesia may pose a risk to the fetus. Child-bearing potential is meant to include all female donors from puberty through menopause. There should be specific documentation of pregnancy assessment in the donor evaluation. Assessment may include a pregnancy test, but a test is

not always required. If a test is not indicated, the rationale should be clearly documented in the medical record (e.g., prior hysterectomy, male donor, etc.)

The inspector should verify that ABO grouping, Rh typing, and pregnancy assessments have been performed according to the Standard and documented.

STANDARD:

C6.7 Laboratory testing on all donors shall be performed by a laboratory accredited or licensed in accordance with applicable U.S. or non-U.S. equivalent regulations using one or more donor screening tests approved or cleared by the FDA or non-U.S. equivalent.

C6.8 ALLOGENEIC DONORS

C6.8.1 In addition to laboratory testing for relevant communicable disease agents as defined in B6.3.2, allogeneic donors shall be evaluated for risk factors for disease transmission by medical history, examination of relevant medical records, and physical examination.

C6.8.2 The medical history shall include at least the following:

C6.8.2.1 Vaccination history.

C6.8.2.2 Travel history.

C6.8.2.3 Blood transfusion history.

C6.8.2.4 Questions to identify persons at high risk for transmission of communicable disease as defined by the FDA or non-U.S. equivalent.

C6.8.2.5 Questions to identify persons at risk of transmitting inherited conditions.

C6.8.2.6 Questions to identify persons at risk of transmitting a hematological or immunological disease.

C6.8.2.7 Questions to identify a past history of malignant disease.

C6.8.3 Allogeneic donors shall be tested for Cytomegalovirus (unless previously documented to be positive).

C6.8.4 Allogeneic donors shall be tested at a minimum for HLA-A, B, DR type by a laboratory accredited by ASHI, EFI, or an affiliate.

C6.8.5 Allogeneic donors shall be tested for red cell compatibility where appropriate.

C6.8.6 Allogeneic donor eligibility, as defined by FDA donor eligibility regulation or non-U.S. equivalent governmental regulation, shall be determined by a physician and shall be documented in the recipient's medical record before the recipient's high dose therapy is initiated and before the donor is mobilized.

C6.8.7 The use of an ineligible allogeneic donor shall require an urgent medical need documentation, including the rationale for his/her selection and suitability by the transplant physician, and the documented informed consent of the donor and the recipient.

C6.8.8 Allogeneic donor eligibility and suitability shall be communicated in writing to the collection and cell processing facilities.

C6.8.9 The donor shall confirm that all the information provided is true to the best of his/her knowledge.

GUIDANCE:
These standards are meant to require the Medical 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.

FACT-JACIE standards and the FDA require that all donors be screened by medical history and risk factors for human transmissible spongiform encephalopathy, Creutzfeldt-Jakob disease, 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 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).

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, and 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 and measles. In those cases in which a potential donor has recently been vaccinated, both the reason for the vaccination and the time interval should be evaluated to estimate the potential risk to a recipient. There should be specific SOPs in dealing with donors who had received smallpox vaccination. Donors must be screened for traveling to the area that would put them at risk for malaria, human transmissible spongiform encephalopathy, SARS (severe acute respiratory syndrome) during periods of world-wide prevalence, or rare strains of HIV, which may not be detected by current screening tests

Cytomegalovirus is considered to be a relevant communicable disease. 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 transplant program should have a clearly defined policy or procedure that addresses the use of CMV-seropositive donors.

STANDARD:
C6.9 DONOR CONSENT

C6.9.1 The collection procedure shall be explained in terms the donor can understand and shall include information about:

C6.9.1.1 The significant risks and benefits of the procedure.

C6.9.1.2 Tests performed to protect the health of the donor and recipient.

C6.9.1.3 The rights of the donor to review the results of such tests.

C6.9.1.4 Alternatives to donation.

C6.9.1.5 Alternative modalities of donation.

C6.9.2 The donor shall have an opportunity to ask questions and the right to refuse to donate.

C6.9.3 Informed consent from the donor shall be obtained and documented by a licensed physician or other health care provider familiar with the collection procedure.

C6.9.4 In the case of a minor donor, informed consent shall be obtained from the donor's parents or legal representative in accord with applicable law and shall be documented.

C6.9.5 The allogeneic donor shall give informed consent and authorization in advance to release the donor's health information to the transplant physician and recipient as appropriate.

C6.9.6 Documentation of consent shall be available to the Collection Facility staff prior to the collection procedure.

GUIDANCE:
The essential elements of informed consent are that the donor, recipient, or patient is told, in terms she or he 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, recipient, or patient 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 inspector may ask to see a consent form to ensure that all the required elements are in place and ask to see the clinic note which details discussion of the protocol. 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.

Often the informed consent to be a donor is the responsibility of the clinical transplant program staff. It is not required that the collection facility have a separate consent form.

C7 LABELS

STANDARD:
C7.1 LABELING OPERATIONS

C7.1.1 Labeling operations shall be conducted in a manner adequate to prevent mislabeling or misidentification of products and product samples.

C7.1.2 The labeling operation shall include, at a minimum, the following controls:

C7.1.2.1 Labels shall be held upon receipt from the manufacturer pending review and proofing against a copy or template approved by the Collection Facility Director or designee to ensure accuracy regarding identity, content, and conformity.

C7.1.2.2 Labels printed on demand at the Collection Facility shall be reviewed against a copy or template approved by the Collection Facility Director or designee to ensure accuracy regarding identity, content, and conformity.

C7.1.2.3 Stocks of unused labels for different products shall be stored in a controlled manner to prevent errors.

C7.1.2.4 Stocks of obsolete labels shall be destroyed.

C7.1.2.5 A system for container label version control shall be employed.

C7.1.2.6 Representative obsolete labels shall be archived for ten (10) years with inclusive dates of use.

C7.1.2.7 A system of checks in labeling procedures shall be used to prevent errors in transferring information to labels.

C7.1.2.8 The information entered on a container label shall be verified by at least two (2) staff members.

C7.1.2.9 All labeling shall be clear, legible, and completed using indelible ink.

C7.1.2.10 The label shall be validated as reliable for storage under the conditions in use.

C7.1.3 Cellular therapy products that are subsequently re-packaged into new containers shall be labeled with new labels when appropriate.

C7.1.4 When the label has been affixed to the container, a sufficient area of the container shall remain uncovered to permit inspection of the contents.

C7.1.5 All data fields on labels shall be completed.

C7.1.6 Labeling elements required by applicable governmental regulations, if any, shall be observed.

C7.1.7 Records to allow tracking of products shall be maintained indefinitely, and include collection or 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.

GUIDANCE:
Label content (discussed below) will have been pre-reviewed by the FACT office 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 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. It is not acceptable to have

different labels stored together with no separation. The inspector should review all relevant labeling SOPs (See C5.1.7). 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

New labels must be placed in a quarantine area upon receipt. The new labels must be inspected for:

- Manufacturing or printing defects
- Form or version number, if applicable
- Legible and correct eye-readable information
- Identity to source (original) label that has been approved for use by the Facility Director or designee

Inspection must include comparison with a label approved by the Collection Facility Director or designee.

These requirements also apply to labels that are printed "on demand," in which case the labels must be reviewed against an approved copy or template at each printing, and this review documented. 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. The process and outcome must be documented prior to release of the labels from the quarantine area. 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.

Only the current version of each label should be available for use in the collection area. 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.

Until *ISBT 128* labels are mandated, the systems in place for constituting the product label differ. 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. 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. 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.

Indelible ink must also be used to record any information entered manually on the label. No fewer than two people must ensure that the manually entered information on the label is accurate. All data fields on a label must be complete; fields for which information is not required must be filled as "NA". 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. The inspector should verify that such labels have been validated for this purpose.

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.

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. 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.

STANDARD:

C7.2 PRODUCT IDENTIFICATION

C7.2.1 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, the donor's medical record, and to all records describing the handling and final disposition of the product.

C7.2.1.1 If a single cellular collection is stored in multiple containers, there shall be a system to identify each container.

C7.2.2 Collection Facilities may designate an additional or supplementary unique numeric or alphanumeric identifier to the cellular product.

C7.2.2.1 Supplementary identifiers shall not obscure the original identifier.

C7.2.2.2 The facility associated with each identifier shall be noted on the label.

C7.2.3 Cellular therapy products shipped by registries may obscure the donor name and collection facility identifiers to maintain confidentiality as long as there is sufficient documentation to allow tracking to the donor.

C7.2.4 Cellular therapy products shall be identified according to the proper name of the product as defined in A3, including the appropriate product modifiers.

GUIDANCE:

The Collection Facility may assign additional identifier(s) to a product; however, it is recommended that no more than two unique product identifiers should 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.

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 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 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 product can be uniquely identified. The essential point is that each 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 tracking to the donor.

Each 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 product from a single donor is divided into multiple containers, each container must be uniquely labeled. This 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.).

The product is additionally identified by its proper name and appropriate modifier as defined in standard A3 under the definition of product. Labels must use the terminology specified in that section. As of this writing, this terminology is consistent with that approved by the International Cellular Therapy Coding and Labeling Advisory Group for *ISBT 128*. See the FACT website for further information regarding implementation of *ISBT 128*: www.factwebsite.org. For further information about *ISBT 128*, see also the ICCBBA website: www.iccbba.org, and recent publications related to the application of *ISBT 128* in cellular therapy. [Ashford, P. et al: Standards for the Terminology and Labeling of Cellular Therapy Products. Transfusion 2007; 47:1319-1327; and Ashford, P. et al: *ISBT 128* Implementation Plan for Cellular Therapy Products. Transfusion 2007; 47:1312-1318.]

STANDARD:

C7.3 LABEL CONTENT

C7.3.1 At the end of any cell collection, the product label on the primary container shall bear the information in the Cellular Therapy Product Labeling Table in Appendix I.

GUIDANCE:

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 if from the applicant Collection Facility or the FACT or JACIE office. 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.

Prescreening of the labels by the FACT or JACIE office staff will be performed and every effort made to correct any deficiencies prior to the on-site inspection. However, it is still the responsibility of the inspector to ensure that the labels in use at the time of inspection comply with the Standards and that the entire labeling process is performed as required. 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 facility 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 product collected, with suitable modifications. Examples of completed labels must not contain blank spaces. “N/A,, or “none” should be used as indicated.

Labeling requirements for the partial label and label at completion of collection are listed in Appendix I of the 3rd edition of FACT-JACIE Standards.

If the 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. 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. Accompanying paperwork should be packaged in a secondary bag with the product for transport to the laboratory 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 laboratory, 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.

An estimate of product volume can be determined by weighing the final product and deducting the weight of the product container.

The Collection Facility address should be explicit enough to correctly identify the location and contact the facility if questions arise or an emergency occurs during processing and/or transportation. For products distributed by an unrelated donor registry, a facility identifier that does not include the Collection Facility name and address should be used to protect donor privacy; however, this information should be part of the laboratory record or be available to the laboratory if needed.

The recommended storage temperature may include ranges, e.g. 0-8º C, 20-26º C, etc.

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. 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
- blue or black indelible ink is recommended.

STANDARD:

C7.4 BIOHAZARD LABEL

C7.4.1 Biohazard labels, as required by applicable laws and regulations, shall be affixed or attached to the product if the collection facility also distributes the product. (See Appendices I and III).

C7.4.2 A biohazard label shall be used if there are reactive test results for relevant communicable disease agents as designated in B6.3.2 or if donor screening indicates the presence of risk factors for relevant communicable disease or disease agents.

GUIDANCE:
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 (as described in C6.3.2) or when the donor screening indicates a risk factor for relevant communicable disease or disease agents. This is required by FACT-JACIE Standards and by cGTP regulations. Biohazard labels should not be applied when testing results are not available or when testing is incomplete at the time the product is labeled. It is not recommended that Biohazard labels be used on all products, since these labels are meant to imply a hazard greater than posed by any biological product.

There have been concerns expressed that use of biohazard labels on the product where it may be observed by non-medical personnel is in violation of Health Insurance Portability and Accountability Act (HIPAA) regulations as interpreted at some institutions. To protect donor confidentiality, biohazard labels may be attached to a product on a tie tag rather than affixed to the bag. If desired, the tie tag can be positioned to minimize its exposure to the casual observer while providing the information needed for program personnel to take additional precautions when needed.

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.

STANDARD:
C7.5 WARNING LABELS

C7.5.1 Warning labels, as defined in Appendices I and III, shall be used as applicable.

C7.5.2 If required by applicable regulations, the following shall be included:

C7.5.2.1 The statement: "Caution: New drug limited by federal law for investigational use only" for products under IND or IDE.

C7.5.2.2 The statement: "Rx Only" for licensed products.

C7.6 Products collected for autologous use shall carry the label: "FOR AUTOLOGOUS USE ONLY" prior to release from the Collection Facility.

GUIDANCE:
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. The exact statements that are required differ for autologous and allogeneic products. The table in Appendix III details the circumstances under which these warnings are required. FACT-JACIE Standards require that autologous as well as allogeneic products be tested for communicable disease (see B6.3.2 and its guidance). However, only allogeneic donors must be screened by medical history for risk factors for disease transmission (see B6.8.2 and its guidance). The GTP regulations, in contrast, require neither donor screening nor testing for autologous donors, but, if such testing is performed, the product must be labeled in accordance with the results. 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 (see Appendix III).

For autologous donors, a complete donor screening for infectious disease risk is not required by these Standards and is not typically performed. 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. 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 inspector should confirm that biohazard labels and warning statements are utilized as described in Appendix III.

Products that are regulated under the FDA 351 regulations must be labeled with the statement “Caution: New drug limited by federal law for investigation use only.” Currently HPC, Apheresis products and HPC, Cord Blood from unrelated donors are regulated under an IND held by NMDP. Such products must contain this statement, attached or affixed to the label or accompanying the product. 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.

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 distribution 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 does not contain all of the elements listed in standard B6.8.2. The statement “Warning: This product may transmit infectious agents” that was required on all product labels by previous editions of FACT-JACIE Standards has been removed and should no longer be used.

STANDARD:

C7.7 LABEL AT COMPLETION OF COLLECTION

C7.7.1 Labeling at the end of collection shall occur before the product is removed from the proximity of the donor.

C7.8 ACCOMPANYING DOCUMENTATION AT DISTRIBUTION

C7.8.1 According to FDA and non-U.S. regulations, as applicable, the following shall accompany the cellular therapy product:

C7.8.1.1 A statement based upon the results of donor screening and testing that the donor has been determined to be eligible or ineligible.

C7.8.1.2 A summary of records used to make the donor eligibility determination.

C7.8.1.3 The name and address of the establishment that made the donor eligibility determination.

C7.8.1.4 A listing and interpretation of the results of all communicable disease screening and testing performed.

C7.8.1.5 A statement that the communicable disease testing was performed by a laboratory certified under CLIA of 1988, as amended from time to time, or has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services (CMS) or has met equivalent non-U.S. requirements.

C7.8.1.6 Instructions for use to prevent the introduction, transmission, or spread of communicable diseases.

C7.8.2 In the case of a donor who has been determined to be ineligible based upon screening or testing there shall be:

C7.8.2.1 A statement noting the reason(s) for the determination of ineligibility.

C7.8.2.2 Documentation of notification of the physician using the product of the results of all testing and screening.

C7.8.3 Product distributed before completion of donor eligibility determination shall be accompanied by:

C7.8.3.1 A statement that the donor eligibility determination has not been completed.

C7.8.3.2 The results of required donor screening or testing that have been completed.

C7.8.3.3 A listing of any required screening or testing that has not yet been completed.

C7.8.3.4 Documentation that the physician using the cellular therapy product was notified that testing or screening was not complete.

GUIDANCE:
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 standards C7.8 and C7.9. 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 standards D8.2 and B7.2) can be used for this purpose. For products that are distributed to another facility, this information must be included (see standard C11.6 for records to be shared when responsibility for the product is divided). If the Collection Facility is responsible for 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 donor eligibility, the Collection Facility must obtain the information from this group so that it may accompany the product. The inspector should review the systems in place that ensure the Collection Facility has access to source data for the information that must be provided at distribution.

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 C7.8 and 21 CFR 1251.55). 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 Collection Facility and is transported to another institution for processing, storage, and/or infusion. 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 www.fda.gov/cber/guidelines.htm.

STANDARD:

C7.9 ADDITIONAL DOCUMENTATION AT OR IMMEDIATELY AFTER DISTRIBUTION

C7.9.1 For 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.

GUIDANCE:

If the Collection Facility participates in donor eligibility determination, completion of this determination must be documented.

C8 CELLULAR THERAPY PRODUCT COLLECTION PROCEDURE

STANDARD:

C8.1 Collection of cellular therapy products shall be performed according to written procedures in the Collection Facility's Standard Operating Procedures Manual.

GUIDANCE:

This standard applies to marrow cells and peripheral blood cells used as HPC and/or as TC.

The inspector should observe a portion of a collection 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 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.

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 and volume 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 transportation of the cells
- methods for detection of clerical errors
- procedures for quality testing.

STANDARD:

C8.2 Before cell collection is undertaken, there shall be a written order from a physician specifying timing, procedural details, and goals of collection.

GUIDANCE:

The physician who initially evaluates the donor and makes the decision to proceed is not always the same one who actually harvests the marrow or collects the peripheral blood stem/progenitor cells by apheresis. 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 or harvest
- 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 SOP
- appropriate authorized signatures
- blood type compatibility for allogeneic transplants
- unexpected red cell antibodies
- recipient weight
- donor weight
- pre and post-collection laboratory result guidelines
- donor medications

STANDARD:

C8.3 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.

C8.3.1 A complete blood count, including platelet count, shall be performed within 24 hours prior to each HPC collection by apheresis.

C8.3.2 There shall be peripheral blood count criteria to proceed with collection.

GUIDANCE:

Day-to-day management of the donor is the responsibility of the 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. 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 to HPC collection and transplantation. 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 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/patient file should be generated in which all pertinent documentation related to the progenitor cell collection or bone marrow harvest may be assembled, including such items as physician orders, consents, worksheets, logs, pre-collection laboratory data, and product transport records. This file may also contain the product processing and disposition records.

STANDARD:

C8.4 General or regional anesthesia, if required, shall be performed or supervised by a licensed, board-certified, or board-eligible anesthesiologist or non-U.S. equivalent.

C8.5 Central venous catheters, where applicable, shall be placed by a licensed physician qualified to perform the procedure.

C8.5.1 Adequacy of line placement shall be verified by the Collection Facility.

GUIDANCE:

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 physician is responsible to obtain central venous access. Credentialing of physicians for this activity is the responsibility of the individual institution. Licensed, qualified, supervised resident physicians are not prohibited by this Standard from placing a central venous access device.

It is ultimately the physician'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 – chest x-ray, fluoroscopy) 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 should be available to the collection team. The collection facility staff should document satisfactory venous access in the donor record.

The inspector should also 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 program.

STANDARD:

C8.6 Administration of mobilization agents shall be under the supervision of a physician experienced in their administration and in the management of complications in persons receiving these agents.

GUIDANCE:

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 physician 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. The interim assessment of donor symptoms related to G-CSF should be performed, and dose adjustments made accordingly.

The inspector should verify that the physician 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.

STANDARD:

C8.7 Methods for collection shall employ procedures validated to result in acceptable cell viability and recovery.

GUIDANCE:

Methods of collection must be validated to result in acceptable progenitor 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 quality management program, are a means of continued validation of collection methods. Any new equipment or collection procedure should be validated prior to implementation and shown to be consistent with or superior to the previous method.

STANDARD:

C8.8 Collection methods shall employ aseptic technique to ensure that cell products do not become contaminated during collection.

GUIDANCE:

Peripheral blood progenitor cells are collected by apheresis procedures utilizing commercially obtained disposable sets with sterile transfer bags approved for human use. Harvested bone marrow is transferred into sterile, commercially available bags approved for human use, or collected in a commercially available set approved for human use. The inspector should verify the use of such approved items by the Collection Facility. 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 laboratory 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 product, and to prevent potential spillage of biohazard material in areas where it may pose a risk to employees, visitors, or patients.

STANDARD:

C8.9 Collection methods for pediatric donors shall employ appropriate age and size adjustments to the procedures.

GUIDANCE:

See guidance for C5.9.

STANDARD:

C8.10 Cellular therapy products shall be packaged in a closed sterile transfer pack appropriate for blood and marrow products.

GUIDANCE:

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. Two knots in the tubing could also suffice if other equipment is unavailable.

STANDARD:

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

GUIDANCE:

Commercially available sets, including a collection bag, in-line 500 and 200 micron filters, and one or more final transfer bags, are available for harvested bone marrow. These should be used with appropriate anticoagulant for collection of cellular therapy products from bone marrow. In-line filters can be replaced during filtration if particulate material in the harvested product clog the filters and restrict flow. The top of the initial collection bag is small and can be closed with a lid; and the assembly is stabilized on a frame, making this system superior for safety and sterility to previously available beakers or flasks. The inspector should verify the use of such approved items by the Collection Facility. 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 laboratory 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 component, and to prevent potential spillage of biohazard material in areas where it may pose a risk to employees, visitors, or patients.

C9 CELLULAR THERAPY PRODUCT STORAGE

STANDARD:

C9.1 Collection Facilities storing cellular therapy products shall control storage areas to prevent mix-ups, deterioration, contamination, cross-contamination, and improper release of products.

C9.2 Collection Facilities storing cellular therapy products shall establish policies for the duration and conditions of storage prior to transfer to a Processing Facility or distribution to a Clinical Program.

GUIDANCE:

The Collection Facility must establish a process to ensure that 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 Collection Facility should define what constitutes storage. Any duration of time between the end of the collection and transport to a Processing Facility or to a recipient for infusion constitutes storage. Particular attention must be paid to the security of the facility and control of temperature and humidity when products are stored in the Collection Facility for extended periods, such as overnight to be transported with a second collection from the same donor. Storage temperature and duration shall be defined by the storing facility and shall include conditions for fresh, cryopreserved, and thawed cellular therapy products. Generally, only fresh products are stored in the Collection Facility. Products that are awaiting release testing results (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., 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 Collection 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. Likewise, transport temperature both from the Collection Facility to the Processing Facility and at distribution must be defined. In the EU, the expiry date must be part of the product information for all tissues and cells.

The inspector should review the 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.

C10 CELLULAR THERAPY PRODUCT TRANSPORTATION

STANDARD:

C10.1 Procedures for transportation 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 product container shall be placed in a secondary container that is sealed to prevent leakage.

C10.1.2 The cellular therapy product shall be shipped to the Processing Facility at a temperature defined in the Collection Facility Standard Operating Procedure Manual.

C10.1.3 Cellular therapy products that are transported from the collection site to any non-contiguous Processing Facility shall be transported 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.

C10.2 The cellular therapy product shall be transported with required accompanying records, as appropriate.

C10.3 There shall be a record of the date and time of product distribution.

GUIDANCE:

Products may be transported from the Collection Facility to a patient care unit or a Processing Laboratory within the same, adjacent, or remote buildings for immediate infusion, processing, or storage. There must be a prospective agreement in place between the relevant Collection Facility, Processing Laboratory, and Clinical Facility regarding transport conditions and the responsibilities of each facility. Procedures for transportation and shipping must be included in an SOP and must address issues of packaging, labeling, temperature, identification, safety, product integrity, and handling for any length of transport.

The product must be packaged to protect it from potential harm during transit and to prevent exposure of individuals involved in its transport to potentially infectious agents. Primary collection bags must be placed in a secondary sealed container such as a zip type bag. It is strongly recommended that when heat sealers are used on the primary container, a minimum of three (3) seals be applied and that secondary containers are also securely sealed. 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, must be considered potentially infectious. For fresh products, absorbent material in the transport container is no longer required by the Standards, but is a recommended practice in the event of breakage. Procedures will vary depending on the transport distance, whether or not the courier and product leave a building, and the nature of the outside transport container.

These procedures must ensure maintenance of optimal temperature during transport. The product temperature during transit is dependent upon a number of variables, including the transport time, the anticoagulants used, and the requirement for further processing. The ideal transport temperature may range from 1-24°C. There must be a prospective agreement among the collecting, processing, and receiving facilities regarding transport conditions. Most products should not be transported at temperatures above 24°C. Products not previously cryopreserved should never be allowed to cool to temperatures below freezing. Transport between facilities that are not adjacent to each other must always use an outer shipping container that protects the product from adverse conditions encountered during transport (air pressure changes, rough handling, etc.), and has been validated to maintain the agreed upon transport temperature. For products transported between sites of a single program, the distance between the collection site and the Processing Facility varies widely. For situations where transport from the collection site to the Processing Facility requires only minutes, as long as the product is transported safely, a controlled temperature environment may not be required. 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 validated outer shipping container. The inspector must determine if the transport procedures in use within the Program are adequate for the conditions.

For non-cryopreserved products, a thermally insulated shipping container should be used with cold packs added as necessary to maintain the required temperature. Documentation of the container temperature at receipt and during transport is also required for the processing records of the receiving facility. Continuous monitoring that creates a record can only be performed using 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 shippers and data loggers.

Containers for transport of products that leave the facility or are transported on public roads must be made of durable material and insulation that will withstand leakage of contents, shocks, pressure changes, and temperature extremes. The containers must be validated prior to use to ensure proper performance for all expected transportation 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.

Transport 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 must include all documentation of donor eligibility as defined in 21 CFR 1271.55 and above (Standards C7.8). Labeling requirements are defined in Standards, Appendix III.

C11 RECORDS

STANDARD:

C11.1 Collection Facility records related to quality control, personnel training or competency, facility maintenance, facility management, or other general facility issues shall be retained for at least ten (10) years by the Collection Facility, or longer in accordance with applicable laws or regulations, or a defined program or institution policy, unless otherwise specified in these standards. Not all records need be immediately available.

GUIDANCE:
Maintenance of records detailed in this standard for 10 years is consistent with the FDA requirements. Records relating to "facility maintenance and management" may be the responsibility of maintenance departments or others outside of the immediate control of the transplant or collection facilities. Agreements should be reached to ensure such record maintenance.

STANDARD:

C11.2 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 governmental laws and regulations, but no less than ten (10) years after the administration of the cellular therapy product, or, if not known, ten (10) years after the date of the distribution, disposition, or expiration of the product, whichever is latest.

C11.3 Employee Records shall be maintained in a confidential manner, as required by applicable governmental laws and regulations.

C11.4 Research records shall be maintained in a confidential manner, as required by applicable governmental laws and regulations, but no less than ten (10) years after the administration, distribution, disposition, or expiration of the cellular therapy product, whichever is latest.

GUIDANCE:
Each Collection Facility has the flexibility to develop individualized systems of maintaining and organizing records as long as certain objectives are achieved. The record keeping system must be documented and should include, but need not be limited to:

- Location of new and completed forms
- Method of error correction that prevents obscuring the original entry and indicates the date and identity of the individual modifying the record
- Method to prevent destruction or loss of the record
- Method of document modifications and distribution
- Time of retention and proper storage location
- System to 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. However, it is recommended that recent records be kept on-site and archived records be readily accessible within a reasonable time frame. Records may be maintained electronically, as original paper records, photocopies, microfiche, or microfilm. Suitable equipment must be available for reading and/or photocopying records maintained on microfiche or microfilm. Electronic records must be backed up on a regular basis and stored to prevent their loss. The Collection Facility must make provisions for all records to be maintained for the required period of time in the event that the Collection Facility ceases operation. Records that allow the tracking of a product from the donor to final disposition and from the recipient to the donor must be maintained even when products are transferred to another facility.

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 U.S. HIPAA regulations or equivalent non-U.S. laws or regulations on confidentiality and data protection. In Europe, the comparable law or regulation is EC 95/46 Directive. This 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 inspector should be alert to breaches in policy that potentially compromise patient or donor confidentiality. Examples 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. The Collection Facility must have SOPs describing the maintenance of donor and recipient confidentiality (See C5.1.1).

Records related to products processed in the 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, Institutional Review Board, and/or governmental authorities may place specific requirements for long-term maintenance of research records. 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.

Since potency and efficacy of the 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. This is most easily accomplished by including a place for initials or other identification on relevant worksheets and forms. 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 Collection Facility should maintain a comprehensive list of all relevant faculty and support staff associated with that facility. The inspector may ask to review the personnel list and dated training or competency records for a specific individual. Likewise, the inspector may ask to see the records of validation of the apheresis instruments. Likewise, retention of records that identify the manufacturers and lot numbers of all reagents and supplies used for collection is critical for tracking purposes in the event of a problem, recall, or adverse event.

Patient files (either electronic or hard copy) must be maintained with a secure system that guarantees absolute confidentiality. Implementation of the HIPAA regulations has led to heightened awareness of patient confidentiality and resulted in a variety of mechanisms to ensure compliance at most institutions. However, the inspector should be alert to breaches in policy that potentially compromise patient confidentiality. Examples include unsecured patient records; patient charts left unattended in areas where restricted personnel and/or visitors may have access; indiscriminate discussion using patient-specific identifiers in the presence of non-medical staff; patient information posted on chalk or bulletin boards that is potentially visible to non-medical staff; and release of confidential information without appropriate consent and approval.

STANDARD:

C11.5 ELECTRONIC RECORDS

C11.5.1 If a computer record-keeping system is used, there shall be a system to ensure the authenticity, integrity, and confidentiality of all records.

C11.5.2 There shall be protection of the records to enable their accurate and ready retrieval throughout the period of record retention.

C11.5.3 There shall be a back-up or alternative system for all electronic records that ensures continuous operation in the event that primary electronic data are not available. The alternative system shall be tested periodically.

C11.5.4 There shall be written procedures for record entry, verification, and revision. A system shall be established for review of data before final acceptance.

C11.5.4.1 The Quality Management Program shall include an assessment of electronic functions to ensure that errors and problems are reported and resolved.

C11.5.5 There shall be a system whereby access to the electronic records is limited to authorized individuals.

C11.5.6 There shall be the ability to generate true copies of the records in both paper and computer format suitable for inspection and review.

C11.5.7 When an electronic system is used, there shall be validated procedures for and documentation of:

C11.5.7.1 Systems development

C11.5.7.2 Numerical designation of system versions if applicable

C11.5.7.3 Prospective validation of system including hardware, software, and databases

C11.5.7.4 Installation of the system

C11.5.7.5 Training and continuing competency of personnel in the use of the system

C11.5.7.6 Monitoring of data integrity

C11.5.7.7 Back-up of the electronic records system on a regular schedule

C11.5.7.8 System maintenance and operations

C11.5.8 All system modifications shall be authorized, documented, and validated prior to implementation.

C11.5.9 The electronic system shall ensure that all donor, product, and patient identifiers are unique.

GUIDANCE:
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. For example, an electronic record of the location of a product in LN2 storage is printed for the processing chart and the information is verified by signature or initial. 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. Each Collection Facility must determine in advance whether the staff will depend on an electronic record or a paper record to perform a regulated activity. This determination should be documented for all records created and maintained by the Collection 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 product and/or the integrity of a record. For example, if a computerized system (word processor) is used

to generate SOPs, validation is not required since the quality and safety of a 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.

The inspector should determine the scope of electronic records used by the Collection Facility and any circumstances where the electronic record is used in lieu of a paper record. Under these circumstances, the inspector should refer to the FDA document *21 CFR Part 11; Electronic Records; Electronic Signatures-Scope and Application*, which is available at *(http:/www.fda.gov/cder/guidance/5667fnl.pdf)* for guidance to assess the validation procedures. Validation procedures under these circumstances are extensive and include such things as:

- Extensive 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, 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
- Verification that the source of data for entry is predefined and consists of original documents whenever possible
- 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

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

STANDARD:

C11.6 RECORDS IN CASE OF DIVIDED RESPONSIBILITY

C11.6.1 If two (2) or more facilities participate in the collection, processing, or transplantation of the product, the records of each facility shall show plainly the extent of its responsibility.

C11.6.2 The Collection Facility shall furnish to the facility of final disposition a copy of all records relating to the collection and processing procedures performed in so far as they concern the safety, purity, and potency of the product involved.

GUIDANCE:

In the event that two or more facilities participate in the collection, processing, or transplantation of a product, the records of each participating facility must clearly indicate the extent of each facility's responsibility. The Collection Facility's records should include relevant contracts and agreements. The entire record of the outside facility(s) need not be duplicated for the Collection Facility record. However, the Collection Facility record should allow tracing/tracking of relevant information to the correct source. For example, the Collection Facility may manufacture products for multiple transplant programs. The Collection 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 reagents lot numbers used for steps performed at the Processing or Clinical Facilities. The Collection Facility should verify that such relevant and appropriate records will be maintained by the facility that performs the work. Records of donor eligibility screening and testing must be provided to the Collection Facility as specified in C7.9. 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/tracing from a donor to a recipient and vice versa. The inspector should determine if divided responsibility occurs regarding any aspect of the transplant process, and ask to review a relevant patient file to confirm that an appropriate mechanism is in place to track the process from beginning to end.

Donor and patient 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 National Marrow Donor Program 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 Collection Facility to furnish to all other facilities involved in the processing and/or infusion of the product any data so far as it concerns the safety, purity, and potency of the product involved. The inspector should review the applicable SOPs regarding dissemination of Collection Facility data and verify that the process is in place.

C12 DIRECT DISTRIBUTION TO CLINICAL PROGRAM

STANDARD:

C12.1 Where cellular therapy products are distributed directly from the Collection Facility to the Clinical Program, without transit via a Processing Facility, the Standards related to labeling, documentation, distribution, transportation, and recordkeeping in Sections D7, D8, D10, D12, and the Appendices apply.

GUIDANCE:
See guidance in referenced sections.

ACCREDITATION MANUAL - SECTION D
CELLULAR THERAPY PRODUCT PROCESSING STANDARDS

D1 GENERAL

STANDARD:

D1.1 These Standards apply to all processing, storage, and distribution activities performed in the Processing Facility.

D1.2 The Processing Facility shall abide by all applicable national and international governmental laws and regulations.

D1.3 The Processing Facility and staff, including a Processing Facility Director and Processing Facility Medical Director, shall have been in place and performing cellular therapy product processing for at least twelve (12) months prior to being eligible for accreditation.

GUIDANCE:

Section D standards apply to the processing of cellular therapy products, regardless of tissue source (bone marrow, umbilical cord blood, peripheral blood, or other tissue source). These Standards also apply to cells derived from any tissue source (marrow, peripheral blood, umbilical cord and placental blood) collected for therapeutic use other than as hematopoietic progenitor cells (Therapeutic Cells).

In the U.S. both HPC and Therapeutic Cell products 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) unless they are extensively manipulated, combined with a device, or their use is non-homologous, in which case 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. It is not the intent of these Standards to address processing of alternative types of stem cells including, but not limited to, embryonic, pancreatic, muscular, mesenchymal, or neuronal which are exclusively regulated under GMP. Although many of the existing standards may be applicable to other types of cellular products, a facility cannot be cited for not following standards in cases where a deviation is recognized as limited to products other than marrow, peripheral blood progenitor cells (PBPC), or Therapeutic Cells.

In the Member States (MS) of the Europe Union (EU), both HPC and Therapeutic Cells 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 EU Directive 2001/83/EC regulates products that are classified as medicinal products (MP). This includes somatic cell therapy MPs and gene therapy MPs. Currently a new regulatory framework on advanced cell therapies is being proposed 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 MS 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.

Compliance with any of the numerous U.S. federal and state regulations or equivalent international regulations [e.g., acceptable FDA audit, state licensure, licensing of tissue establishments by the Member State in the EU, Clinical Laboratory Improvement Act (CLIA), Occupational Safety and Health Administration (OSHA)], or accreditation by the American Association of Blood Banks (AABB), American Society for Histocompatibility and Immunogenetics/European Foundation for Immunogenetics (ASHI/EFI), or the College of American Pathologists (CAP) or 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. However, compliance with other organization's standards or governmental regulations does not imply that FACT-JACIE Standards have been met. In all cases, governmental regulations supersede any organization's standards. The inspector should review current certifications to ascertain what areas of facility function have been certified by other organizations and/or competent authorities.

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 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. 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 inspection.

D2 PROCESSING FACILITY

STANDARD:

D2.1 Where required, the Processing Facility shall be registered with the FDA or non-U.S. equivalent for the activities performed.

GUIDANCE:

Establishments that are involved with the recovery, screening, testing, packaging, processing, storage, labeling, or distribution of cellular therapy products in the United States, are required to register with the FDA yearly (21 CFR 207, 807, and 1271). This registration requires a listing of the activities in which the Processing Facility engages and a listing of each type of cell therapy product that is regulated under GTP or regulated as medical devices, drugs, or biological drugs (21 CFR 207 and 807). Products that fall under this requirement include: HPC, Apheresis; HPC, Cord Blood; and Therapeutic Cells. HPC, Marrow is excluded if it is minimally manipulated, not combined with a drug or a device, and is for homologous use. More information regarding the requirements and process for FDA registration can be found at: http://www.fda.gov/cber/tissue/tisreg.htm. Note that each activity performed by the institution must be registered, regardless of who performs the activity. A Processing Facility that is within a larger institution such as a hospital or medical center may combine its registration with other services related to the same regulations. Activities that may be performed by a collection facility include the apheresis collection procedure screening of donors for infectious disease risk to determine eligibility, and temporary storage of products.

In the EU, the competent authorities in the Member State 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.

The inspector should look for documentation of FDA registration within the U.S., or documentation of a similar registration that may be required outside of the U.S. A copy of the validated FDA registration document 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. A copy may not be immediately available in the Processing 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 FDA during the on-site inspection.

STANDARD:

D2.2 The Processing Facility shall be of adequate space, design, and location for the intended procedures.

D2.2.1 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.

D2.2.2 The Processing Facility shall be secure to prevent the admittance of unauthorized personnel.

D2.2.3 The Processing Facility shall provide adequate lighting, ventilation, plumbing, drainage, and access to sinks and toilets to prevent the introduction, transmission, or spread of communicable disease.

GUIDANCE:

The inspector will tour the Processing Facility during the on-site inspection, including all locations where products are received, processed, stored, and distributed. The inspector should observe the organization, design, location, and amount of space to determine if the Processing Facility is adequate for the number and types of procedures it performs. The physical plant should include ample lighting, a temperature controlled environment, and access to hand-washing and toilet facilities. There should be clearly designated areas for product receipt, labeling, and storage that are separate from the processing area. Inspectors should ask personnel to describe where each of these activities is typically performed and how a product moves through the Processing Facility. The inspector should inquire as to how the Processing 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. A cluttered Processing Facility without a defined workflow is evidence that the Processing Facility does not have adequate space or is poorly designed.

If research activities are performed in the proximity of the Processing Facility, the facility must demonstrate adequate separation of processing and research activities. Products, supplies and reagents must be clearly segregated either by physical methods or by proper use of signage.

The Processing Facility must be locked, or otherwise secured, when not in use. At all times, access to the facility shall be limited to approved personnel. Limited access can be maintained through appropriate signage and by installation of locks that limit entry to only authorized individuals. Video monitoring is an alternative and/or complementary method of limiting access to the facility. The inspector must verify that some system is in place to prevent unauthorized persons from entering the facility. The inspector should confirm that the Processing Facility is located in an area accessible only to authorized personnel. In addition, the inspector should verify the following: there is appropriate signage throughout the facility, the Processing Facility is locked after working hours, personnel wear proper identification badges, and that the management designations of the Processing Facility are described within an SOP (See D5.1.23).

STANDARD:

D2.3 There shall be adequate equipment for the procedures performed at the Processing Facility.

D2.4 There shall be a process to control storage areas to prevent mix-ups, contamination, and cross contamination of all products during quarantine and prior to release or transport.

GUIDANCE:
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.

Examples include:

- Sharing a biological safety cabinet for the purpose of cell processing with a microbiology laboratory.
- 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 also used for food or beverage.
- Performing different procedures on multiple products in the same biological safety cabinet simultaneously.

If research activities are performed using equipment shared with the Processing Facility, the Processing Facility must demonstrate that adequate procedures are in place to prevent product contamination or cross contamination.

If the Processing Facility has only a single piece of critical equipment, such as a single biosafety cabinet or a single centrifuge, that is otherwise adequate for the work being performed, then a back-up plan must be in place in the event of equipment failure. See also standard D5.1.17. 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.

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.

If the location of the liquid nitrogen freezers prohibits limited access (i.e., 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/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.

STANDARD:
D2.5 SAFETY REQUIREMENTS

D2.5.1 The Processing Facility shall be operated in a manner to minimize risks to the health and safety of employees, patients, donors, and visitors.

D2.5.2 Instructions for action in case of exposure to communicable disease or to chemical, biologic, or radiological hazards shall be included in the safety manual.

D2.5.3 Medical waste shall be disposed of in a manner that minimizes any hazard to facility personnel and to the environment in accordance with applicable governmental laws and regulations.

D2.5.4 The Facility shall be maintained in a clean, sanitary, and orderly manner.

D2.5.5 Gloves and protective clothing shall be worn while handling biological specimens. Such protective clothing shall not be worn outside the work area.

GUIDANCE:
These Standards apply to all facilities involved in cellular therapy product therapy (Clinical Programs, Collection, and Processing Facilities). 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. The facility policies and procedures, including housekeeping and waste disposal, must document consistency with good biosafety procedures, including adherence to universal precautions and to federal, state, or provincial regulations regarding safety.

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 product and/or patient. The use of personal protective attire must be defined by an SOP (See D5.1.26). There must clearly be demonstrated policies and procedures for a general chemical safety plan (See D5.1.27).

Any potentially biohazardous material shall be discarded in a safe manner according to written protocols for the disposal of biohazard waste (See D5.1.28). Contaminated materials may be discarded by autoclaving, ultra-high temperature incineration, decontamination with hypochlorite solution, and, in some locations, the use of a landfill. Radioactive waste must be discarded using methods approved by appropriate governmental agencies. Also, facilities should post warning signs wherever radioactive materials are in use. Facility personnel responsible for these activities should be identified.

Each facility shall have a safety manual readily available in the Processing Facility (See D5.1.29). 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. The facility may keep a condensed or summarized hard copy of the institutional safety manual in the Processing Facility. In this case, there must be written documentation of how the safety manual is kept updated with institutional revisions. Alternatively, an SOP that defines the location of hard copies of the institutional safety manual, in the event of computer failure, will suffice. 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. Safety, infection control or biohazard waste disposal procedures that are unique to the Processing Facility must be covered in a Processing Facility SOP manual.

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. The inspector should examine how products are being handled and discarded (e.g., incinerator, waste field, etc.) and compare his/her observations with the written protocols. Compliance with national and international regulations should be addressed by the 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.

D3 PERSONNEL

STANDARD:

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 Medical Director, if appropriately credentialed.

D3.1.2 The Processing Facility Director shall be responsible for all procedures and administrative operations of the Processing Facility, including compliance with these Standards.

D3.1.3 The Processing Facility Director shall participate regularly in educational activities related to the field of cellular processing and/or transplantation.

D3.2 PROCESSING FACILITY MEDICAL DIRECTOR

D3.2.1 There shall be a Processing Facility Medical Director who is a licensed physician with postgraduate training and/or one year's 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.

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

D3.2.3 The Processing Facility Medical Director shall participate regularly in educational activities related to the field of cellular processing and/or transplantation.

GUIDANCE:

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 experience in cellular therapy product processing. The period of experience is not defined but must include all of the activities performed within the Processing Facility. Since standard D1.3 requires the Processing Facility and the Processing Facility Director to have been processing products minimally one year, experience of one year is expected. The Processing Facility Director is responsible for all procedures and administrative operations of the Cell Processing Facility including compliance with the FACT-JACIE Standards and with all other applicable laws and regulations including in the EU the responsibility for providing information to the competent authorities. Specific duties of the Processing Facility Director, or designee approved by the Processing Facility Director, required by these Standards includes:

- 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
- Approval of new and modified SOPs prior to implementation and annually
- Definition of test and procedures for cellular 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 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/or one year's experience in the preparation and clinical use of cellular therapy products. To fulfill this standard, the Medical Director must provide a photocopy of his/her current national and/or local governmental license. Since documentation of the M.D. 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 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 product infusion
- Authorization for the distribution of non-conforming products and products released due to urgent medical need
- Review and approval of clinically relevant laboratory SOPs
- Approval of medically relevant planned and unplanned deviations from SOPs
- Notification when medically relevant end-points are not achieved
- Authorization for product discard

The Processing Facility Director and Medical Directors 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 local governmental laws or regulations. 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). Experience can consist of time spent in training in another facility and/or on-the-job training. The Processing Facility and Processing Facility Medical Directors are required to participate regularly in educational activities related to the processing and use of cellular therapy products. To assess participation in educational activities, the inspector may ask about membership in professional organizations, publications in peer-reviewed journals, and/or attendance at meetings and workshops. The Processing Facility and Medical Directors are required to submit 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. The Processing Facility and Processing Facility Medical Directors may have other responsibilities, but s/he or a designee should be available to facility personnel at all times. The Processing Facility and Medical Director responsibilities should be outlined in a job description or the procedure manual for the Processing Facility.

STANDARD:

*D3.3 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 Fac*ility.

D3.3.1 The Processing Facility Quality Management Supervisor shall participate regularly in educational activities related to the field of cellular processing and/or quality management.

D3.4 OTHER STAFF

D3.4.1 The Processing Facility shall have an adequate number of trained staff for the volume and complexity of all operations.

GUIDANCE:
The Processing Facility must identify at least one person with the responsibility of 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 QM Supervisor must have an active role in reviewing and approving Standard Operating Procedures (SOPs) and must ensure that the procedures are in compliance with FACT-JACIE Standards 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. FACT does not prohibit the QM Supervisor from participating in Processing 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 s/he is solely responsible. For small programs, 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 control procedures. SOPs should clearly define the role(s) of the Processing Facility Director the QM Supervisor and other QM personnel in the QM program. 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. The Processing Facility Quality Management Supervisor is required to participate regularly in educational activities related to cell processing and the quality management of cellular therapy products. To assess participation in educational activities, the inspector may ask about membership in professional organizations, publications in peer-reviewed journals, and/or attendance at meetings and workshops.

Parallel to standards D2.2 and D2.3 requiring adequate facility space and equipment, there must also be sufficient technical and other support staff for the scope and number of services provided. Personnel responsible for cell processing must be adequately trained and supervised, and their continued competence must be documented. 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. 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. The Inspector should confirm the documentation of continued competency assessment. It may also be useful to talk directly with the technical personnel regarding workload requirements and the adequacy of staffing.

D4 QUALITY MANAGEMENT

STANDARD:

D4.1 The Processing Facility shall establish and maintain a written Quality Management Plan that includes a process for controlling and monitoring the manufacturing of cellular therapy products that ensures that products conform to specifications, are not contaminated, and maintain function and integrity. The plan shall address, at a minimum:

- *D4.1.1 Organizational structure*
- *D4.1.2 Agreements*
- *D4.1.3 Process development and review*
- *D4.1.4 Personnel qualifications, training, and competency*
- *D4.1.5 Outcome analysis*
- *D4.1.6 Audits*
- *D4.1.7 Management of cellular therapy products with positive microbial cultures*
- *D4.1.8 Detection and reporting of errors, accidents, and adverse events*
- *D4.1.9 Record review and document control*
- *D4.1.10 Validation of reagents, equipment, and procedures*

D4.1.11 Qualification of facilities, reagents, supplies, and equipment
D4.1.12 Inventory control
D4.1.13 Product tracking
D4.1.14 Process control

GUIDANCE:
Development of a written comprehensive Quality Management (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 broadened the scope of requirements of the Quality Plan for the Processing Facility to be more in line 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 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.

There must be a written QM plan that includes all of the elements listed in standards D4.1.1 through D4.1.14. 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 to the appropriate document where it is described. The QM Plan does not necessarily need to be stand-alone, serving only the Processing Facility. 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 Transplant Program may have one QM Plan that addresses all aspects of the Clinical Program, 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. However, it remains the responsibility of the Processing Facility to ensure that all elements of the QM Program required in part D4 are in place and functioning and that documentation of compliance to standards that are not performed by Processing Facility staff is available to the facility.

The written QM plan for the Processing Facility will be provided to the inspector in prior to the on-site inspection. The thoroughness and attention to detail of the written QM plan is an indication of how QM is perceived and executed within the program. An incomplete or poorly written QM plan is an indication that QM is not deemed an integral and important component of the program. Under these circumstances, the inspector should pay particular attention to evaluating the QM efforts of the program during the on-site inspection process. The inspector should specifically look for documentation of compliance for QM activities not directly performed by Processing Facility staff.

STANDARD:
D4.2 The Processing Facility Director shall be responsible for the Quality Management Plan as it pertains to the Processing Facility. The performance of this activity may be delegated to a designated individual(s) with the appropriate training, knowledge, and expertise.

D4.2.1 The designated individual(s) shall have authority over and responsibility for ensuring that the Quality Management Plan is effectively established and maintained.

D4.2.2 The designated individual(s) shall not have oversight of his/her own work if this person also performs other tasks in the Processing Facility.

D4.2.3 The designated individual(s) shall report on quality management activities, at a minimum, quarterly.

D4.2.4 The designated individual(s) shall provide a report on the performance of the Quality Management Plan, at a minimum, annually to the Processing Facility Director and, if applicable, the Clinical Program Director.

GUIDANCE:
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. The same person may be responsible for QM of all components of the 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. The identified responsible person should not be directly responsible for review of work they performed. 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.

The inspector should ask to see evidence that the outcome of Quality Assessments is communicated to key individuals within all participating entities in the program. Communication is most effectively accomplished by regularly scheduled QM meetings. 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.

STANDARD:
D4.3 The Quality Management Plan shall include an organizational chart of key personnel and functions within the Processing Facility.

D4.3.1 The Quality Management Plan shall include a description of how these key personnel interact to implement the Quality Management activities.

GUIDANCE:
The organizational chart should include the reporting structure for the Processing Facility QM Program. 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. The description of the operation of the quality program should include the mechanisms (meetings), participants, schedule, and documentation. 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 program. The inspector should review any documents that support the described organizational structure. The documentation should include the names and responsibilities of all critical staff. Lines of responsibility and communications must be clearly defined in a way that is understood by all involved. The organizational chart for the entire program, as well as for the Processing Facility, will be provided to the inspector prior to the on-site inspection. The inspector will verify that the organization and daily function is as described.

STANDARD:

D4.4 The Quality Management Plan shall include policies and procedures for development and implementation of written agreements with third parties whose services impact the cellular therapy product.

GUIDANCE:

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. If agreements exist, examples should be reviewed by the inspector for adherence to the established process. Such agreements may include, but are not limited to donor qualification, determination of donor suitability and eligibility, procurement (collection) of the 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.

How such agreements are executed is a function of the type of Processing Facility. That is, 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. In all cases a process must exist for the development and implementation of such agreements.

In the event the Processing Facility (or entities with which the Processing Facility has agreements) terminates their 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.

STANDARD:

D4.5 The Quality Management Plan shall include methods for process development, approval, validation, implementation, review, revision, and archiving for all critical processes, policies, and procedures.

GUIDANCE:

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 Program needs to identify the documents critical to the Processing 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 receipt into the laboratory, other processes may require multiple documents for its performance. 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 program 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. Standard D4.5 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.

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

STANDARD:

D4.5.1 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 and preventive action.

GUIDANCE:

Quality management involves ongoing assessment of the stability, reproducibility, and effectiveness of critical processes in order to improve continually 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.

STANDARD:

D4.6 The Quality Management Plan shall include personnel requirements for each position in the Processing Facility. Personnel requirements shall include at a minimum:

D4.6.1 Current job description for all staff

D4.6.2 A system to document the following for each staff member:

D4.6.2.1 Initial qualifications

D4.6.2.2 Orientation

D4.6.2.3 Initial training

D4.6.2.4 Competency for each function performed

D4.6.2.5 Continued competency at least annually

D4.6.2.6 Provisions for continuing education, training, and retraining

D4.6.3 The Quality Management Plan shall include a description of minimal trainer qualifications and a uniform plan for staff training.

GUIDANCE:
Personnel requirements are to be included in the Processing Facility QM plan and should ensure that each position has specified job duties and responsibilities. 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.

Organization-specific issues are generally covered by orientation programs, but this should be confirmed by the inspector. Legal and regulatory context can be demonstrated by including training related to GTP, GMP, and FACT-JACIE Standards.

The inspector should review procedures or policies describing the elements of staff training and continued competency as described in standards D4.6.2.1 through D4.6.2.6. Initial qualifications generally include minimal educational requirements or formal training 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 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 defined by an SOP (See D5.1.15). 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 training plan SOP should also define the minimal qualifications of any designated trainers.

STANDARD:
D4.7 The Quality Management Plan shall include a process for documentation and review of product efficacy, and outcome analysis, as appropriate, including at least:

D4.7.1 For HPC products, a process for documentation and review of time to engraftment following product administration.

GUIDANCE:
Outcome analysis involves the collection, evaluation and distribution of patient outcome data, including engraftment in the case of HPC products. Acceptable criteria for each product should be developed by the Processing Facility in conjunction with the clinical team and this process defined by an SOP (See D5.1.21). 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 Processing Facility should initiate corrective action. The inspector should confirm documentation of all activities from definition of expected outcome to process improvement, when indicated.

Timely engraftment of the HPC product in a recipient following a myeloablative 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 Processing Facility or presented by another section of the Clinical Program at a common quality management meeting where Processing Facility personnel are in attendance. The inspector should ask to see the engraftment data and/or minutes of meetings, including the personnel in attendance, where engraftment data are presented. If a Processing Facility provides products to one or more Clinical Programs, it is the responsibility of the Processing 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 Processing Facility to have (or provide) access to this data to both the Clinical Program and the Collection Facility.

STANDARD:

D4.8 The Quality Management Plan shall include a process and timetable for conducting independent quality audits of the Processing Facility's activities to verify compliance with elements of the Quality Management Program.

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

D4.8.2 Audit results shall be reviewed, reported, and documented, at a minimum, on a quarterly basis.

D4.8.3 The results of audits shall be used to recognize problems, detect trends, and identify improvement opportunities.

GUIDANCE:

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. 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 head of the Processing Facility Quality Program should identify areas to be audited and audit frequency. Standard D4.8.2 indicates that audits should be performed minimally on a quarterly basis. This does not mean that the same audit is performed quarterly, rather the audit process should be performed throughout the year with quarterly review and reporting 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 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. The process by which the Processing Facility performs audits must be defined by an SOP (See D5.1.22)

Examples of audits in 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 laboratory cleaning before, after, and between products

There should be evidence that audit reports are shared with the Processing Facility staff, the Processing Facility Director and Medical Director as appropriate, and the Program Director, Collection Facility Directors, and others with potential interest. The inspector should review the audit process and example audits to determine 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.

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.

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.).

STANDARD:

D4.9 The Quality Management Plan shall include policies and procedures on the management of cellular therapy products with positive microbial culture results that address at least:

D4.9.1 Documentation and product labeling

D4.9.2 Release of the product from the distribution facility, including identification of authorized individuals and criteria for product release

D4.9.3 Investigation of cause

D4.9.4 Notification of transplant physician, Collection Facility and/or Cell Processing Facility, as applicable

D4.9.5 Notification of the recipient prior to infusion

D4.9.6 Recipient follow-up and outcome analysis

D4.9.7 Follow up of the donor, if relevant

D4.9.8 Reporting to regulatory agencies, if appropriate

GUIDANCE:

The Transplant Program must develop an integrated approach to the management of cellular therapy products with positive microbial culture results that are identified either before or after the products have been infused. Policies and procedures are required in all three areas of the transplant program – clinical, collection, and laboratory. These Standards list the topics that must be addressed in policies, but do not dictate a single policy 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.

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 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. In the U.S., regulations for 351 and 361 products should be followed and the program should have policies that cover responsibility for reporting. Labeling requirements may be defined by the institution and should include requirements for the use of a biohazard label and warning statements. 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 other cases a positive result may only become available after the product has been infused. The laboratory is usually the first facility to be notified of a positive culture result. There should be timely notification of the Collection Facility, which should in turn investigate all records related to that collection to determine if anything in the collection process could have contributed to the positive culture result.

The 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.

STANDARD:

D4.10 The Quality Management Plan shall include a system for detecting, evaluating, documenting, and reporting errors, accidents, suspected adverse events, biological product deviations, variances, and complaints.

D4.10.1 Documentation of each adverse event associated with the cellular therapy product shall be reviewed by the Processing Facility Director and/or Medical Director, as appropriate.

D4.10.2 Adverse events associated with the cellular therapy product shall be documented in a manner that complies with institutional requirements and applicable governmental laws and regulations.

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 Deviations from Standard Operating Procedures shall be documented.

D4.10.4.1 Planned deviations shall be pre-approved by the Processing Facility Director or designee and if medically relevant, by the Processing Facility Medical Director.

D4.10.4.2 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.

D4.10.5 Corrective actions shall be implemented as appropriate. These shall include both short-term action to address the immediate problem and long-term action to prevent the problem's recurrence.

D4.10.6 Effectiveness of corrective actions shall be verified.

D4.10.7 When applicable, the event shall be reported to appropriate regulatory agencies.

D4.10.8 There shall be policies and procedures to document and follow-up customer-reported product failures, concerns, or complaints.

GUIDANCE:
There must be a mechanism 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 Processing Facility should define errors, accidents, deviations, adverse reactions, and complaints in an SOP (See D5.1.18 and D5.1.19) along with when and how each is reported.

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.

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.

It is recommended that programs and laboratories 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. The inspector should ask to see SOPs that describe how adverse reactions are detected, investigated and reported, files of adverse reactions, and evidence that adverse reactions are reviewed by the Processing Facility Director and reported as appropriate, to the Clinical Program Director, the transmitting facility and appropriate governmental agencies.

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 Program or by other policies or procedures and must be defined in an SOP (See D5.1.11). The most common biological product deviations encountered involve products with a positive microbial culture (as described in the guidance for standard D4.9) or products from ineligible donors. Specific issues regarding products from ineligible donors are addressed in the guidance for standard D6.2.

If there is a complaint of 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 re-occurrence as defined by an SOP (See D5.1.20). 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.

STANDARD:

D4.11 The Quality Management Plan shall include a mechanism for document control and for regular review of records relating to cellular product processing, storage, release, and transportation. The document control system shall include at a minimum the following elements:

D4.11.1 Definition and current listing of all critical documents that must adhere to the document control system requirements.

D4.11.2 Assignment of a numeric or alphanumeric identifier to each document regulated within the system.

D4.11.3 A procedure for document approval, including the date, signature of approving individual(s), and the effective date.

D4.11.4 A system to ensure that controlled documents cannot undergo accidental or unauthorized modification.

D4.11.5 A system for documentation of training associated with each procedure and its revisions.

D4.11.6 A system for document change control that includes a description of the change, the signature of approving individual(s), approval dates, and effective date.

D4.11.7 A system for the retraction of obsolete documents to prevent unintended use.

D4.11.7.1 Obsolete documents shall be archived for a minimum of ten (10) years.

D4.11.8 A system for record creation, assembly, storage, archival, and retrieval.

GUIDANCE:
This standard primarily addresses the need for a comprehensive document control system that covers all of the critical documents used by the Processing Facility. Documents that fall under this system should be listed and minimally include:

- Policies
- Procedures
- Labels
- Worksheets and checklists
- Forms

The document control system must include the assignment of a unique identifier for each individual document and document version, the creation and approval process, a method to prevent unintended modification, a mechanism for training, control of document changes, and a system for document use, assembly, storage, archival and retrieval. The Processing Facility Director should determine which documents fall under this system.

The inspector should confirm that a written change control policy exists and is effective to prevent unintended changes to processes, policies, or SOPs. 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 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 requirement for timely record review is also addressed in standard D6.8. Refer to the guidance for that section for further information.

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

STANDARD:
D4.12 The Quality Management Plan shall include a process for product tracking that allows tracking from the donor to the recipient or final distribution and from the recipient, or final disposition, to the donor.

GUIDANCE:
One of the most important paper trails in the Processing Facility allows for tracking of information about the cellular therapy product at all steps between the donor and the patient. Documentation in the processing record should include the identity and content of the cellular therapy product, the unique identification of the donor, the 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 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 (D5.1.12).

The Inspector should review examples of final labeled products and determine if tracing and tracking from the donor selection through final product is possible. All critical steps should identify who performed the step or action and when it was completed.

STANDARD:

D4.13 The Quality Management Plan shall include a mechanism to ensure continuous operations in the event that the electronic record system ceases to function, including a plan for data backup, and to ensure compliance with applicable laws.

GUIDANCE:

The inspector should review policies and forms to be used in case the electronic record keeping system is unavailable. 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. The inspector should determine if products can be produced to the same standard of quality even if the electronic records are not available.

STANDARD:

D4.14 The Quality Management Plan shall include a process for validation and verification of critical reagents, equipment, and procedures.

D4.14.1 There shall be documentation of review and acceptance of validation studies by the appropriate individual from Quality Management.

D4.14.2 Changes to a process shall be verified or validated to ensure that they do not create an adverse impact anywhere in the operation.

D4.14.3 Procedures for manufacturing reagents in-house shall be validated.

GUIDANCE:

Validation is confirmation by examination and provision of objective evidence that specific requirements can be consistently fulfilled. 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 at a minimum:
a) Processing procedures (D4.14.2, D6.3, D6.13.1)
b) Equipment used for processing, release testing, or transport (D10.3, D10.4.4, D10.4.5.1)
c) Reagents made on-site and those not approved for human use (D4.14.3)
d) Labels (D7.1.2.10)
e) Electronic records system, if applicable (D12.2.7, D12.2.8)

The inspector should ask to see the SOPs for conducting validation studies. 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 inspector should review a sampling of validation studies of the facility, processes, reagents and equipment. 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 inspector should note poorly designed or inadequately performed validation studies during the review process. The validation studies must include documented review by the QM Supervisor and/or other appropriate individuals from Quality Management.

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 human 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 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.

Reagents generated in-house for use in progenitor cell processing must be validated.

STANDARD:

D4.15 The Quality Management Plan shall include a process for qualification of critical supplies, reagents, equipment, procedures, and facilities.

D4.15.1 Critical procedures shall include at least the following: processing techniques, cryopreservation protocols, storage conditions, and transportation.

D4.15.2 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 cellular product function and integrity.

D4.15.3 Supplies and reagents used in the processing, testing, cryopreservation, storage, and administration of cellular therapy products shall be stored at the appropriate temperature in a secure, sanitary, and orderly manner.

D4.15.4 All supplies and reagents coming into contact with cellular therapy products during processing, storage, and/or administration shall be sterile and of appropriate grade for the intended use.

D4.15.4.1 Reagents that are not of the appropriate grade shall undergo qualification for the intended use.

D4.15.4.2 Non-disposable supplies or instruments shall be cleaned and sterilized using a procedure verified to remove infectious agents.

D4.15.5 Supplies and reagents should be used in a manner consistent with instructions provided by the manufacturer.

D4.15.6 There shall be a process to prevent the use of expired reagents, supplies, and obsolete labels.

GUIDANCE:
Quality can be maintained only if there is control over critical supplies, reagents, equipment, procedures, and the facility itself. Qualification is defined in these Standards as "The establishment of confidence that processes, equipment, and reagents function consistently within established limits." Here the Standards define the critical procedures that must be qualified, even after validation, to include procedures for the processing, testing, cryopreservation, storage, and transport of cellular therapy products. For example a change in a critical reagent used for cryopreservation, such as DMSO would require that the cryopreservation procedure be qualified to ensure that the change has not affected quality of the product. Likewise, a change in equipment to a new controlled rate freezer might require qualification of the freezing program to ensure that the freezing parameters meet the predetermined specifications. Procedure qualification can be performed by determining expected outcomes at critical steps and monitoring that these outcomes are achieved, by establishing the 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 D5.1.17). SOPs for cryopreservation and thawing procedures are specifically required by standard D5.1.5.

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. The simultaneous presence of products for more than one patient in a facility is not an infrequent occurrence requiring that procedures be in place to prevent such mix-ups (See D5.1.3). Other, more specific, standards require practices to minimize this likelihood. The inspector should observe the Processing Facility in operation, if possible, or should question personnel regarding the procedures in place when multiple products are undergoing processing and the procedures used for sequential processing. Questions may be asked to determine: Are products from different patients in the biological safety cabinet at the same time? Is equipment used to process more than one product (e.g., centrifuges)? Are reagents identified as dedicated to a single processing procedure? Is there a record of the lot numbers and expiration dates for all reagents used in processing? How is cleaning and disinfection performed between processing procedures?

Once received, supplies and reagents used for processing must be stored in a manner that preserves their function and sterility. The inspector should observe storage areas and confirm that supplies and reagents are stored under the conditions specified by the manufacturer. For items requiring storage at a specified temperature range, the temperature of the storage area must be monitored and documented. When refrigerators and freezers 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. This 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.

Whenever possible supplies and reagents that come into contact with cellular therapy products should be clinical grade, and must be free of microbial contamination. If a supply or reagent is not clinical grade (i.e., labeled for research only), it should be of the highest grade (or purity) available and the Processing Facility must have demonstrated that the supply or reagent functions consistently within the established limits. The inspector should review how such reagents or supplies were qualified. Use of supplies and reagents according to manufacturer's instructions is recommended, when possible and appropriate.

For some specialized processing procedures, equipment or instruments that come into contact with the 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. The inspector should review the records of this verification process.

There should be a mechanism to monitor the flow of supplies and reagents within the facility to prevent the use of outdated supplies and reagents. 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. 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. 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.

STANDARD:

D4.15.7 There shall be a system to uniquely identify and track all critical equipment used in the processing of cellular therapy products.

D4.15.8 Equipment used in the processing, testing, cryopreservation, storage, transportation, and administration of cellular therapy products shall be maintained in a clean and orderly manner and located to facilitate cleaning, calibration, and maintenance.

D4.15.9 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.

D4.15.10 Equipment shall conform to applicable governmental laws, legislation, and regulations.

GUIDANCE:

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 that might affect product quality must be identified and tracked. For this purpose, standard D4.15.7 requires that there be a system by which the critical equipment can be uniquely identified. 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. In parallel to the standard for supplies and reagents, it is also important that the system in use allow for the identification of all cell therapy products processed using a given piece of critical equipment.

Equipment used for processing 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 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. Schedules may vary among laboratories, based on frequency of use, performance stability, or recommendations from the manufacturer. It is recommended that recent records of regularly scheduled maintenance and quality control be readily available for each piece of equipment. Tags or stickers should be visible on the equipment indicating that QC parameters have been met, the date QC testing was performed and when it 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. 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 D5.1.17). 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. 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 D5.1.24). This is important to prevent microbial contamination of products, as well as to prevent transmission of infectious disease and cross-contamination. The inspector should confirm by visual inspection that equipment can be easily accessed for cleaning and maintenance.

EUD 2006/17/EC Annex IV 1.3.10 specifies that where possible, equipment that is compliant with the CE Marking Directive are 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, see http://ec.europa.eu/enterprise/newapproach/legislation/guide/.

STANDARD:

D4.15.11 Critical facility parameters that may affect cellular therapy product processing, storage, or release shall be identified, controlled, monitored, and recorded to demonstrate ongoing compliance.

D4.15.12 There shall be documentation of facility cleaning and sanitation, environmental conditions, and inspection of environmental control systems to ensure adequate conditions for proper operations.

D4.15.12.1 Records of all cleaning and sanitation activities performed to prevent product contamination shall be maintained ten (10) years after their creation.

GUIDANCE:

The Processing Facility must identify the facility parameters that should be controlled and monitored based on their potential effect on product quality. The typical HPC Processing Facility may not require a qualified environment for the facility provided that processing steps requiring exposure to the environment are performed in a biosafety cabinet (See standard D6.5.1). However, a facility that extensively manipulates products and performs procedures with many "open" steps may require a greater level of environmental control. Environmental monitors for controlled space should include measures of air quality such as particle counts and microbial colony counts and may also require control of humidity and temperature. EU guidelines are more specific, requiring 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 Enterprise Directorate "EC Guide to Good Manufacturing Practice Revision to Annex 1", Brussels, May 30, 2003, for additional information. This guide may be found at: http://www.hpci.ch/files/documents/guidelines/hh_gl_gmp.pdf. Contaminants in the 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). There must be ongoing monitoring of any parameters that have been determined to be critical and these should be defined by an SOP (See D5.1.23 and D5.1.25) and compliance documented through quality records.

Processing Facility cleaning and sanitation must be performed on a regular basis in order to prevent contamination and cross-contamination of product. The methods used must be specified by an SOP (See D5.1.24). 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 ceiling also fall under this standard. The Processing Facility, together with the cleaning services vendor must establish SOPs for this activity. Facility cleaning must be documented and the records maintained for 10 years.

STANDARD:

D4.16 The Quality Management Plan shall include a process for inventory control that encompasses reagents, supplies, labels, products, and product samples.

D4.16.1 There shall be a system to uniquely identify and track all critical reagents, supplies, and labels used to manufacture cellular therapy products.

D4.16.2 Each supply and reagent used to manufacture and administer cellular therapy products shall be examined visually for damage or evidence of contamination upon receipt.

GUIDANCE:

The inspector should confirm that there is a process in place to determine acceptability of all critical materials (reagents, supplies, labels, products, and product samples) before they are accepted into inventory and made available for use. This process must be described in an SOP (See D5.1.16). Critical materials must be defined by the Processing Facility and tracked. 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 processing record must include the identity of the supplies and reagents that were used.

Each product must be assigned a unique alphanumeric identifier that is part of the inventory control system. Generally, the product inventory and reagent and supply inventory are separately managed. Product samples 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 inspector should review the inventory control process and documentation of supply and reagent examinations at receipt. The system in use may utilize an electronic system or a log book to enter all incoming supplies and materials. The system must include documentation that materials under the inventory control system meet predefined facility requirements.

STANDARD:

D4.17 The Quality Management Plan shall include a process for controlling and monitoring the manufacturing of cellular therapy products to ensure products meet predetermined release specifications.

D4.17.1 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.

D4.17.2 Communicable disease testing required by these Standards shall be performed using FDA approved tests in an FDA or non-U.S. equivalent registered laboratory, that is accredited or licensed in accordance with applicable governmental regulations.

D4.17.3 Other tests required by these Standards, not performed by the Processing Facility, shall be performed by a laboratory certified by CMS, CLIA, or non-U.S. equivalent.

D4.17.4 For tests performed within the Processing Facility, there shall be documentation of on-going 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.

D4.17.5 Cellular therapy products that do not meet release or 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.

D4.17.5.1 Notification of the recipient's physician of testing and screening results for ineligible donors shall be documented.

GUIDANCE:
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 be easily 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 D5.1.2).

The Processing Facility Director is responsible for defining release criteria for 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 D5.1.9). 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
- HLA typing (allogeneic only)
- ABO group and Rh typing at collection
- Microbial testing after processing
- Post-processing TNC and viability
- Post processing CD34 cell assay for HPC products
- Assay of target cell population for products that have been enriched or depleted

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. The inspector should review processing records to determine if all required testing was performed within the required time frame and if the results are recorded. Documentation that the 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.

Some of the specified testing may be performed by an external laboratory. Communicable disease testing is specifically required by cGTP regulations to be performed using test kits approved for donor screening by the FDA in a CLIA-accredited or FDA-registered laboratory or non-U.S. equivalent

laboratory that is accredited or licensed according to local governmental regulations. Since communicable disease testing is usually facilitated by the Clinical Program or Collection Facility prior to collection, the Processing Facility must have a system in place whereby these results are available to the Processing Facility. Communicable disease test results and verification that testing was in compliance with the requirements of standard D4.17.2 must be available for review by the inspector. Other testing not performed by the Processing Facility must be performed by a laboratory certified by CMS, CLIA, or the non-U.S equivalent. Such laboratories must have valid and current licenses and accreditation. At a minimum, the ASHI or EFI certification of the relevant laboratory performing histocompatibility testing, will have been sent to the inspector in advance. These documents do not necessarily have to be available on-site in the Processing Facility, but documentation that they exist must be reviewed by the inspector. This can take the form of certification and accreditation information on test results reports.

For testing that is performed within the Processing Facility, laboratory personnel are required to participate in proficiency testing programs (when available) for the procedures and/or tests that they perform. Examples 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 Processing 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. If the facility is performing testing that is usually considered to be outside of the normal activities of a Processing Facility, the inspector must verify that those activities have been inspected by the appropriate regulatory body (e.g., CAP, CLIA, or ASHI/EFI) and that the facility is approved to perform those activities. Examples include: a) microbiology testing, b) histocompatibility testing, c) infectious disease marker testing, and d) chimerism studies.

D5 POLICIES AND PROCEDURES

STANDARD:

D5.1 The Processing Facility shall have documented policies and procedures addressing all appropriate aspects of operations and management including at a minimum:

D5.1.1 Product receipt

D5.1.2 Processing and process control

D5.1.3 Prevention of cross-contamination

D5.1.4 Red cell compatibility testing and processing of ABO-incompatible products

D5.1.5 Cryopreservation and thawing

D5.1.6 Labeling (including associated forms and samples)

D5.1.7 Expiration dates

D5.1.8 Storage (including alternative storage if the primary storage device fails)

D5.1.9 Release and exceptional release

D5.1.10 Product recall

D5.1.11 Biological product deviations

D5.1.12 Product tracking

D5.1.13 Transportation

D5.1.14 Quality management and improvement

D5.1.15 Personnel training and competency assessment

D5.1.16 Reagent and supply management

D5.1.17 Equipment maintenance, monitoring, and corrective actions in the event of failure

D5.1.18 Errors, accidents, and adverse events

D5.1.19 Complaints

D5.1.20 Corrective actions

D5.1.21 Outcome analysis

D5.1.22 Audits

D5.1.23 Facility management

D5.1.24 Cleaning and sanitation procedures

D5.1.25 Environmental control

D5.1.26 Hygiene and use of personal protective attire

D5.1.27 Infection control, biosafety, chemical, and radiological safety

D5.1.28 Decontamination and disposal of medical and biohazard waste

D5.1.29 Emergency and safety

D5.1.30 Disaster plan

D5.1.31 Donor and recipient confidentiality

GUIDANCE:
The standard requires that each Processing Facility have written policies and procedures that comprehensively address all important aspects of the Processing Facility. The Processing 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. 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 standards D5.1 and the facility's own procedure manual. The items listed in Standard D5.1 include the minimum requirements; a Processing Facility may exceed these requirements, but not omit any of these.

The policies and procedures must be detailed, unambiguous, and adequately define all operational aspects of the Processing Facility. The minimum elements that must be included in a policy or

procedure are listed in Standard D5.2 and D5.3. The policies and procedures can be generated within the Processing Facility or in collaboration with other institutional infrastructures. This applies most often to SOPs addressing safety, infection control, biohazard disposal, radiation safety, and planned emergency response to disasters. In cases where institutional policies and procedures are inadequate to meet standards or where there are issues that are specific to the Processing Facility, the facility must develop its own policies and procedures (See D5.1.30). In situations where institutional policies and procedures are utilized, there must be a defined mechanism for initial and annual review and approval of all revisions within the Processing Facility.

The written copy or electronic version (with provisions for hard copies as necessary) of the Processing Facility'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 in use must be identical to the source document and must not be used to alter, modify, extend, delete or otherwise edit any Standard Operating Procedure. This should be verified by 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 Processing Facility. The inspector should verify the procedure for development and review for all policies and procedures is being followed.

There will not be time to read all policies and procedures during the on-site inspection. The inspector will be 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 evidence of implementation of written procedures and other activities that can only be verified in person at the inspection site.

STANDARD:

D5.2 The Processing Facility shall maintain a detailed Standard Operating Procedures Manual. The Standard Operating Procedures Manual shall include:

D5.2.1 A procedure for preparing, reviewing, disseminating, implementing, and revising procedures.

D5.2.2 A standardized format for procedures, including worksheets, reports, and forms.

D5.2.3 A system of numbering and/or titling of individual procedures, policies, worksheets, and forms.

GUIDANCE:

The SOP manual must have a Standard Operating Procedure outlining the method by which the Processing Facility creates, approves, implements, reviews, and updates its SOPs (the "SOP for SOPs"). 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 Processing Facility 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. 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 "SOP for SOPs" adheres to the requirements for all controlled documents as specified in standard D4.11. 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 facility's standard SOP format.

STANDARD:

D5.3 Procedures shall be sufficiently detailed and unambiguous to allow qualified technical staff to follow and complete the procedures successfully. Each individual procedure requires:

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, including diagrams and tables, as needed.

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.

D5.3.7 Documented approval of each procedure and procedural modification by the Processing Facility Director or Medical Director, as appropriate, prior to implementation and annually thereafter.

D5.3.8 Copies of current versions of orders, worksheets, reports, labels, and forms, where applicable.

GUIDANCE:

This Standard defines the minimum elements required in each SOP. 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 somewhere.

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 CLSI Website. The CLSI format is not required. The facility may use the format of its choice, as long as all listed elements are present. Some 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) or from the Canadian Standards Association website (www.csa-international.org).

Copies of 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 may be prudent to attach one or more completed forms to illustrate possible real life scenarios. Although not required by FACT-JACIE 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.

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, plasma volume, etc. The range for a given parameter can be determined

within the Processing Facility by evaluating data from its own products. Determination of a mean ± 1 or 2 standard deviations defines an acceptable range.

FACT-JACIE Standards require documented annual review of each procedure by the Processing Facility Director or by the Medical Director 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 annual review 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. 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:

D5.4 Copies of the Standard Operating Procedures Manual shall be readily available to the facility staff at all times.

GUIDANCE:

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 Processing Facility. 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.

STANDARD:

D5.5 All personnel in the facility shall follow the Standard Operating Procedures detailed in the manual.

D5.6 New and revised policies and procedures shall be reviewed by the staff prior to implementation. This review and associated training shall be documented.

GUIDANCE:

Personnel are required to adhere to the approved SOPs in their manual. Although only annual review is required, when conditions require that a procedure or practice be modified, SOP review and revision must occur in a timely fashion. Documentation that staff have reviewed new and revised procedures and received appropriate training before the procedures are implemented should be reviewed by the inspector. 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 implementation. Training guides specific to each procedure and to any major revision also facilitate documentation of appropriate training of staff.

STANDARD:

D5.7 Archived procedures, including 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.

GUIDANCE:

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. The inspector should review the SOP archival system, including local requirements.

STANDARD:

D5.8 Standard Operating Procedures for all procedures shall comply with these Standards and all applicable governmental regulations.

GUIDANCE:

While the Processing Facility is expected to adhere to their own operating procedures, those procedures must be in compliance with these Standards and with applicable governmental regulations. A more stringent local standard is acceptable, but not one that contradicts FACT or governmental requirements.

D6 PROCESS CONTROLS

STANDARD:

D6.1 There shall be a written request from the recipient's physician before processing is initiated specifying the product type, recipient and donor identifier, the type of processing that is to be performed, and the anticipated date of processing.

GUIDANCE:

Section 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.

Before processing begins, a physician's order must be received by the Processing Facility and must specify how and when the product should be processed as well as the identifier 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. Examples 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. Stored products from more than one donor collected for a given patient 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. The inspector should review the physician order form in use and verify that it contains the required elements.

STANDARD:

D6.2 Information required by the Processing Facility prior to distribution of the cellular therapy product shall include:

D6.2.1 A statement of donor eligibility and suitability.

D6.2.2 For ineligible donors, the reason for their ineligibility.

D6.2.3 Documentation of urgent medical need and physician approval for use, if applicable.

GUIDANCE:

Before the Processing Facility can distribute the cellular therapy product for infusion, GTP regulations require that donor eligibility and suitability be confirmed. This determination is not generally performed by the Processing Facility, but rather by the Clinical Program or Collection Program. In order to distribute the product after processing, donor eligibility and suitability information must be obtained from the facility making that determination. For 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 patient has approved. See the guidance for section D7.9 for additional information regarding product distribution from the Processing Facility.

STANDARD:

D6.3 Processing procedures shall be validated in the Processing Facility and documented to result in acceptable target cell viability and recovery.

D6.3.1 Published validated processes shall be verified within the Processing Facility prior to implementation.

D6.4 Critical control points and associated assays shall be identified and performed on each product as defined in Standard Operating Procedures.

GUIDANCE:

The Processing Facility Director should determine what and how processing methods will be validated. Validation may be retrospective, concurrent, or prospective. For standard procedures that were adopted and implemented prior to establishment of FACT-JACIE 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. 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 annually 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 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 patient. It is not the position of the inspector to request validation for procedures that have not yet been unequivocally validated by the scientific community. 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 the procedure 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 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. The inspector must review one or more validation or verification studies to ensure these are being performed as required by these Standards.

As specified in standard D4.17.1, 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. The inspector should specifically review that all testing procedures are defined by SOPs.

STANDARD:

D6.5 Methods for processing shall employ aseptic technique and cellular therapy products shall be processed in a manner that minimizes the risk of cross-contamination.

D6.5.1 Where processing of tissues and cells involves exposure to the environment, processing shall take place in an environment with specified air quality and cleanliness.

D6.5.2 The effectiveness of measures to avoid contamination and cross-contamination shall be verified and monitored.

D6.6 The Processing Facility shall monitor and document microbial contamination of cellular therapy products after processing, as specified in Standard Operating Procedures.

D6.6.1 The results of microbial cultures shall be reviewed by the Processing Facility Director or designee in a timely manner.

D6.6.2 The recipient's physician shall be notified in a timely manner of any positive microbial cultures.

GUIDANCE:

The inspector should determine (from direct observation and/or by reviewing SOPs) that aseptic technique is utilized during processing. 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 products. GTP regulations specifically forbid the pooling of products from more than one donor during processing. 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.

Any portion of a processing protocol performed outside of a closed system should be carried out in an environment with appropriately classified air quality (such as a Biological Safety Cabinet) in addition to being closely monitored for sterility. 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. Biological safety cabinets should be routinely monitored for airflow and regularly maintained to ensure the proper functioning of filters. Measures of air quality such as particle counts and microbial colony counts are additional ways to verify the effectiveness of measures to avoid contamination and cross-contamination.

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.

Note: The equivalent of a Grade A environment is a Class 100 air cleanliness classification. The equivalent of a Grade D environment is a Class 100,000 air cleanliness classification.

It is a requirement that microbial testing be performed post-processing at a minimum. 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. 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. Additional training in aseptic techniques and/or modification of cleaning protocols may be appropriate. Gram stains of 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 1-2 weeks before final culture reports are available for Processing Facility Director (or designee) review. The inspector should look for systems that allow immediate notification of the Processing Facility when a culture tests positive. It is the responsibility of the Processing Facility to ensure that the patient's physician is notified of positive culture results in a timely manner. 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 products that have been cryopreserved. Cryopreserved HPC grafts 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. 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.

STANDARD:

D6.7 Worksheets shall be completed concurrently with processing and shall be maintained for all procedures.

D6.7.1 The individual responsible for each significant step of processing shall be documented.

D6.7.2 Lot numbers, expiration dates, and manufacturer of critical reagents, supplies, and identification of key equipment used in each procedure shall be documented.

D6.8 The Processing Facility Director or designee shall review the processing record for each cellular therapy product prior to release.

D6.8.1 The recipient's physician and the Processing Facility Medical Director shall be notified when the clinically relevant processing end-points are not met.

*D6.8.2 Notification and appropriate remedial actions, if taken, shall be documented in the processing recor*d.

GUIDANCE:

Worksheets 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. For example, cryopreservation of a bone marrow harvest may include: 1) receipt of the product into the 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. 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.

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 product in the case of an adverse event. 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. 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 facility at a given time may be part of an inventory control program. The inspector may observe a random sample of reagents in use to document that these are in-date and appropriately labeled.

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. 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. Other records may be reviewed within a reasonable time after processing. Examples include: a) sterility testing results, b) flow cytometry, 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 patient 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 patient 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.

The inspector should ask to see written procedures that describe the review process and indicate by whom and when the review takes place. Patient 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 products that failed to meet specifications so the inspector can determine how the situation was resolved. Resolution 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 patient outcome data (i.e., engraftment, GVHD, or infection) and notification of appropriate individuals

STANDARD:

D6.9 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 governmental laws and regulations.

GUIDANCE:

Minimal manipulation is defined by the FDA as "processing that does not alter the relevant biological

characteristics of cells or tissues". If procedures are performed in the Processing Facility using other than minimal manipulation, the inspector should inquire if IRB and the appropriate IND or IDE approval has been obtained. Likewise, recipients must sign consent forms for any graft manipulation beyond minimal as defined by the FACT-JACIE Standards and existing governmental laws and regulations. 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 patient should still consent to the procedure. In most institutions, consent forms are not part of the laboratory chart record; instead, consent forms are part of the patient 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. Assurance of patient safety and the ability to conduct responsible research are equally important goals central to the mission of FACT-JACIE.

STANDARD:

D6.10 For allogeneic products, a test for the ABO group and Rh type shall be performed on each product or on blood obtained from the donor at the time of collection.

D6.10.1 If there are previous records, there shall be a comparison of ABO group and Rh type with the last available record. Any discrepancies shall be resolved and documented prior to issue of the product.

D6.11 For autologous products, a test for ABO group and Rh type shall be performed on the first product or on blood obtained from the donor at the time of first collection.

GUIDANCE:

ABO group and Rh typing of cellular therapy products are performed for two reasons, one of which is to serve as an identity check that can be quickly compared with previous records to reduce the risk of processing a product from the wrong donor. This is especially important when more than one collection is performed or if the collected product is transported from one center to another. This record check must be performed before the product is issued for infusion. For autologous donors this requirement remains for the first collection, but is optional for subsequent collections. However, it is important to note that if typing was not performed on the product or on blood collected from the donor at the time of donation, the ABO group and Rh type may not be present on the label. The inspector should confirm that the ABO group and Rh type testing is being performed and should verify the process by which this information is compared to previous records.

The second reason product ABO group and Rh typing is performed on allogeneic products is to avoid the unintentional use of ABO incompatible products containing RBCs that might result in a transfusion reaction. These Standards do not dictate how ABO and Rh incompatible 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 standard D5.1.4). 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 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. Infusion procedures for allogeneic products should include a confirmation of the ABO group and Rh type of both the product (through a label check) and the recipient (from the patient chart). For this reason, allogeneic donors must be tested each day of collection for ABO group and Rh type.

STANDARD:

D6.12 For cryopreserved products, aliquot(s) shall be stored under conditions that ensure a valid representation of the clinical product and shall be available for testing, if required.

GUIDANCE:

The Standards require that one or more aliquots of individual HPC collections be cryopreserved and stored under conditions that allow the sample to represent the product. Such samples should be stored at the same temperature range of the product. It is preferred but not required that the aliquot be stored in the same freezer so as to represent not only the product freezing conditions but also the storage conditions. The method by which 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 residual 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. Processing Facility Directors 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 but often include: the assessment of viability and cell recovery, CFU content, and CD34 content. Whatever testing is performed must be specified in the cryopreservation SOP and those tests must be validated and controlled as described in standard D6.13.1.

STANDARD:

D6.13 Laboratory processes shall include:

D6.13.1 The establishment of appropriate and validated assays and test procedures for the evaluation of cellular therapy products.

D6.13.1.1 For all cellular therapy products, a total nucleated cell count and viability measurement shall be performed.

D6.13.1.2 For HPC products, a CD-34 assay shall be performed.

D6.13.1.3 For products undergoing manipulation that alters the final cell population, a relevant and validated assay, where available, should be employed for evaluation of the target cell population before and after the processing procedures.

D6.13.2 Provisions for monitoring the reliability, accuracy, precision, and performance of laboratory test procedures and instruments.

D6.13.3 A documented system for the identification and handling of test samples so that they are accurately related to the corresponding product, donor, or recipient, as applicable.

GUIDANCE:

A limited number of assays are required by FACT-JACIE Standards: 1) TNC, 2) Viability, 3) Post-processing assessment of CD34 cells for HPC products, 4) Monitoring assays for target populations after enrichment or depletion, along with those required elsewhere including 5) Post-processing microbial cultures (D6.6), 6) ABO group and Rh typing from donor blood at collection or from the product itself (D6.10), and 7) Communicable disease testing within specified time limits before collection (B6.3.2 & D4.17.2). Additional tests and test intervals other than those required are to be determined by the Processing Facility. Requirements of the facility providing these testing services, including the

Processing Facility itself, are addressed in standard D4.17 and its guidance. 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. 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 a Processing Facility, the inspector should verify that SOPs are in place, that there is a record of method validation, 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 products being tested.

Standard D6.13.1.1 requires assessment of total nucleated cell count and product viability, but unlike earlier versions of FACT-JACIE Standards, does not specify 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 a procedure requiring minimal manipulation has been validated to demonstrate that reproducible recovery of cells occurs, it may be argued that subsequent cell counts post-processing are unnecessary. 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 recommend that additional cell counting and viability assessment be performed during and/or post-processing.

The requirement for CD34 cell assessment of HPC products is new to this edition of Standards. As for TNC and viability, the standard does not specify when this testing is to be performed, but for the same reasons discussed in the previous paragraph, such testing should be performed after processing. Assessment of CD34 cell content at the end of collection may also be valuable in determining the effect of processing on CD34 cell content, and if processing is minimal, may be sufficient to predict CD34 cell content in the infused product. 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. 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 (Usually below 5×10^6 for platelets and 2×10^6 for granulocytes). Review of the CD34 cell content at the end of processing in conjunction with outcome analysis of time to engraftment should be used, especially for patients whose engraftment appears to be delayed.

Assays to monitor products should measure one or more target cell population before and after any manipulation when assays are used for products that undergo processing which alters the final cell population, usually enrichment or purging procedures. For HPC products, such assays should also include the CD34 cell population. The inspector should review adequacy of the methods and the validation of processing procedures that alter the final cell population.

To determine that test samples can be appropriately linked to donor and/or recipient, the inspector should observe how sample tubes are labeled and distributed for testing and how results are posted. It is recommended that test sample labels include the product unique identifier. The SOPs for a given processing procedure must indicate what tests are required and when during a procedure they are performed. The test results should be immediately available for review, preferably in the patient's file.

D7 LABELS

STANDARD:

D7.1 LABELING OPERATIONS

D7.1.1 Labeling operations shall be conducted in a manner adequate to prevent mislabeling or misidentification of products and product samples.

D7.1.2 The labeling operation shall include, at a minimum, the following controls:

D7.1.2.1 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.

D7.1.2.2 Labels printed on demand at the Processing Facility shall be reviewed against a copy or template approved by the Processing Facility Director or designee to ensure accuracy regarding identity, content, and conformity.

D7.1.2.3 Stocks of unused labels for different cellular products shall be stored in a controlled manner to prevent errors.

D7.1.2.4 Stocks of obsolete labels shall be destroyed.

D7.1.2.5 A system for container label version control shall be employed.

D7.1.2.6 Representative obsolete labels shall be archived for ten (10) years with inclusive dates of use.

D7.1.2.7 A system of checks in labeling procedures shall be used to prevent errors in transferring information to labels.

D7.1.2.8 The information entered on a container label shall be verified by at least two (2) staff members prior to release of product.

D7.1.2.9 All labeling shall be clear, legible, and completed using indelible ink.

D7.1.2.10 The label shall be validated as reliable for storage under the conditions in use.

D7.1.3 Cellular products that are subsequently re-packaged into new containers shall be labeled with new labels, when appropriate.

D7.1.4 When the label has been affixed to the container, a sufficient area of the container shall remain uncovered to permit inspection of the contents.

D7.1.5 All data fields on labels shall be completed.

D7.1.6 Labeling elements required by applicable governmental regulations, if any, shall be observed.

D7.1.7 Records to allow tracking of products shall be maintained indefinitely, and include collection or 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.

GUIDANCE:
Label content (discussed below) will have been pre-reviewed by the FACT office 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 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. It is not acceptable to have different labels stored together with no separation. The inspector should review all relevant labeling SOPs (See D5.1.6). 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

New labels must be placed in a quarantine area upon receipt. The new labels must be inspected for:

- Manufacturing or printing defects
- Form or version number, if applicable
- Legible and correct eye-readable information
- Identity to source (original) label that has been approved for use by the Processing Facility Director or designee

Inspection must include comparison with a label approved by the Processing Facility Director or designee

These requirements also apply to labels that are printed “on demand”, in which case the labels must be reviewed against an approved copy or template at each printing, and this review documented. 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. The process and outcome must be documented prior to release of the labels from the quarantine area. 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.

Only the current version of each label should be available for use in the processing area. 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.

Until *ISBT 128* labels are mandated, the systems in place for constituting the product label differ. 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. 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. 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.

Indelible ink must also be used to record any information entered manually on the label. No fewer than two people must ensure that the manually entered information on the label is accurate. All data fields on a label must be complete; fields for which information is not required must be filled as "NA". 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. The inspector should verify that such labels have been validated for this purpose.

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.

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. 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.

STANDARD:

D7.2 PRODUCT IDENTIFICATION

D7.2.1 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, the donor's medical record, and to all records describing the handling and final disposition of the product.

D7.2.1.1 If a single cellular collection is stored in multiple containers, there shall be a system to identify each container.

D7.2.2 Facilities may designate an additional or supplementary unique numeric or alphanumeric identifier to the cellular product.

D7.2.2.1 Supplementary identifiers shall not obscure the original identifier.

D7.2.2.2 The facility associated with each identifier shall be noted on the label.

D7.2.3 Cellular therapy products shipped by registries may obscure the donor name and collection facility identifiers to maintain confidentiality as long as there is sufficient documentation to allow tracking to the donor.

D7.2.4 Cellular products shall be identified according to the proper name of the product as defined in A3, including the appropriate product modifiers.

D7.2.4.1 Significant modifications made to the cellular product subsequent to collection and prior to cryopreservation shall be noted.

GUIDANCE:

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. 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 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 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. The essential point is that each 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 tracking to the donor.

Each 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 product from a single donor is divided into multiple containers, each container must be uniquely labeled. This 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.).

The product is additionally identified by its proper name and appropriate modifier as defined in standard A3 under the definition of product. Labels must use the terminology specified in that section. As of this writing, this terminology is consistent with that approved by the International Cellular Therapy Coding and Labeling Advisory Group for *ISBT 128*. See the FACT website for further information regarding implementation of *ISBT 128*: www.factwebsite.org. For further information about *ISBT 128*, see also the ICCBBA website: www.iccbba.org, and recent publications related to the application of *ISBT 128* in cellular therapy. [Ashford, P. et al: Standards for the Terminology and Labeling of Cellular Therapy Products. Transfusion 2007; 47:1319-1327; and Ashford, P. et al: *ISBT 128* Implementation Plan for Cellular Therapy Products. Transfusion 2007; 47:1312-1218.]

STANDARD:

D7.3 LABEL CONTENT

D7.3.1 Each label shall include at least the elements detailed in the Cellular Therapy Product Labeling Table in Appendix I.

GUIDANCE:

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 if from the applicant Processing Facility or the FACT or JACIE office. 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.

Prescreening of the labels by the FACT or JACIE office staff will be performed and every effort made to correct any deficiencies prior to the on-site inspection. However, it is still the responsibility of the inspector to ensure that the labels in use at the time of inspection comply with the Standards and that the

entire labeling process is performed as required. 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 provided to the inspector prior to the inspection and correspond to the labels in the facility 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 product collected, with suitable modifications. Examples of completed labels must not contain blank spaces. “N/A,, or “none” should be used as indicated.

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. 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. Accompanying paperwork should be packaged in a secondary bag with the product for transport to the laboratory 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.

Labels at the completion of collection are the responsibility of the collection program, so are not specifically listed in the Processing Facility section. Processing Facilities that supply these labels to the collection site should refer to Appendix I of the 3rd edition of FACT-JACIE Standards for the requirements and to the Collection Facility guidance for specific issues regarding collection labels.

STANDARD:

D7.4 PARTIAL LABEL

D7.4.1 If the 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.

D7.4.2 Minimally, the information required in D7.4.1 shall be present on the product during all stages of processing.

D7.4.3 Any container bearing a partial label shall be accompanied by the information required in Appendix I. Such information shall be attached securely to the product on a tie tag or enclosed in a sealed package to accompany the product.

GUIDANCE:

If the Processing Facility utilizes a partial label, the inspector must ensure that the labeling SOP (required by standard D5.1.6) 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. Additional information may be attached to the product via a tie tag; however, it is acceptable to have additional information on accompanying paperwork as long as the paperwork is included in the secondary bag (i.e., zip lock bag) with the product. It is not acceptable to transport multiple product bags from different donors using partial labels in a single secondary bag or with all of the additional information on a single inventory sheet. Labels applied during processing may utilize partial labels (In Process labels). This is the only case where partial labels are acceptable without additional information in an enclosed secondary container. Appropriate modifiers should be applied to the label while it is undergoing different stages of processing to ensure that other qualified lab personnel can identify which steps in the process have been completed.

STANDARD:

D7.5 BIOHAZARD LABEL

D7.5.1 Biohazard labels as required by applicable regulations, shall be affixed or attached to the product when the product is distributed. (See Appendices I & III)

D7.5.2 A biohazard label shall be used if there are reactive test results for relevant communicable disease agents as designated in B6.3.2 or if donor screening indicates the presence of a risk factor for relevant communicable disease or disease agents.

GUIDANCE:

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 (as described in B6.3.2) or when the donor screening indicates a risk factor for relevant communicable disease or disease agents. This is required by FACT-JACIE Standards and by cGTP regulations. Biohazard labels should not be applied when testing results are not available or when testing is incomplete at the time the product is labeled. It is not recommended that Biohazard labels be used on all products, since these labels are meant to imply a hazard greater than posed by any biological product.

There have been concerns expressed that use of Biohazard labels on the product where it may be observed by non-medical personnel is in violation of Health Insurance Portability and Accountability Act (HIPAA) regulations as interpreted at some institutions. To protect donor confidentiality, biohazard labels may be attached to a product on a tie tag rather than affixed to the bag. If desired, the tie tag can be positioned to minimize its exposure to the casual observer while providing the information needed for program personnel to take additional precautions when needed. As a result, labels attached (via tie tag) may be preferred over affixed labels. In such cases, the tie tag can be positioned to minimize its exposure to the casual observer while providing the information needed for program personnel to take additional precautions when needed. 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.

STANDARD:

D7.6 WARNING LABELS

D7.6.1 Warning labels, as defined in Appendices I and III, shall be used, as applicable.

D7.6.2 Products collected for autologous use shall carry the label: "FOR AUTOLOGOUS USE ONLY".

GUIDANCE:

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. The exact statements that are required differ for autologous and allogeneic products. The table in Appendix III details the circumstances under which these warnings are required. FACT-JACIE Standards require that autologous as well as allogeneic products be tested for communicable disease (see B6.3.2 and its guidance). However, only allogeneic donors must be screened by medical history for risk factors for disease transmission (see B6.8.2 and its guidance). The GTP regulations, in contrast, require neither donor screening nor testing for autologous donors, but if such testing is performed the product must be labeled in accordance with the results. 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 (see Appendix III).

For autologous donors, since a complete donor screening for infectious disease risk is not required by these Standards and is not typically performed, if the complete donor screenings not performed 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 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. 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 inspector should confirm that biohazard labels and warning statements are utilized as described in Appendix III. 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 standard B6.8.2. The statement "Warning: This product may transmit infectious agents" that was required on all product labels by previous editions of FACT-JACIE Standards, has been removed and should no longer be used.

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 distribution 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.

STANDARD:

D7.7 LABELING AT COMPLETION OF PROCESSING

D7.7.1 At the end of processing, the label on the product container shall bear the information in the Cellular Therapy Product Labeling Table in Appendix I.

GUIDANCE:

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 allogeneic products, the numeric/alphanumeric donor identifier must be attached or affixed to the label; if no numeric/alphanumeric identifier is assigned (as is often the case for first degree related donors), the donor name must be attached or affixed to the label. For unrelated donors, this identifier may be assigned by the donor registry; for related donors, an identifier other than the donor name may be assigned at the time of collection. As long as this identifier can be traced to the donor medical records, a name is not required. The donor identifier must be distinguished from the product identifier, which is assigned for each collection day. See the guidance for standard D7.2 for a further discussion of product and donor identifiers.

The product proper name must include the modifiers appropriate for the processing that was performed. The name and modifier(s) 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. Expiration dates and times are not dictated by the FACT-JACIE Standards. However, 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 D5.1.7). The inspector should look for evidence and justification of expiration dates and times on all products. 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, this information must be part of the Processing Facility record or be available to the Processing Facility, if needed. The donor registry information should include the name of the registry, not just the fact that it is an unrelated registry.

Product volume may be determined by weighing the final product and deducting the weight of the product container. Calculations to convert grams to milliliters may or may not be performed, according to the Processing Facility SOPs. The labeled volume should be within 10% of the true volume.

The name, volume, or concentration of residual anticoagulant or other additives used during processing must be attached or affixed to the label. 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 recommended storage temperature should include acceptable ranges, e.g., 2-8°C, 20-26°C, <-135°C, etc.

Appropriate biohazard labels and warning statements are required as specified in Appendix III.

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. ABO typing may not have been performed on products collected from autologous donors after the first day of collection as allowed by standard D6.11. In such cases ABO group and Rh type information will not be available. Note that for the ABO group and Rh type to appear on the product label, testing of blood from the product or from the donor at the time of collection must have been performed. Given the potential for transfusion reactions due to the presence of ABO incompatible red blood cells, products from allogeneic donors must be tested each day of collection.

STANDARD:

D7.8 LABELING PRIOR TO DISTRIBUTION

D7.8.1 At the time of distribution, the label on the product container shall bear the information in the Cellular Therapy Product Labeling Table in Appendix I.

D7.8.2 Products distributed from donors for whom donor eligibility determination is incomplete shall bear the statement: "Not Evaluated For Infectious Substances".

D7.8.2.1 Products from allogeneic donors shall also bear the statement: "Warning: Advise Patient of Communicable Disease Risks".

D7.8.3 The name and address of the facility that determines that the 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.

GUIDANCE:

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 standard D5.1.4, see also standard D6.10 and its associated guidance). The inspector should review this process.

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).

Although it is not specified by these Standards, it may be useful to include the total nucleated cell number on HPC product labels at distribution and the total number of T cells or T cells/kg patient body weight affixed or attached to the TC-T cell product label. 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.

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 Appendix III. It is important for the processing staff to verify the accuracy of the donor/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
- The label is not damaged or defaced

In addition, there should be a documented verification of patient and donor identity prior to issue.

STANDARD:

D7.9 ACCOMPANYING DOCUMENTATION AT DISTRIBUTION

D7.9.1 According to FDA and non-U.S. regulations as applicable, the following shall accompany the cellular therapy product:

D7.9.1.1 A statement, based upon the results of donor screening and testing, that the donor has been determined to be either eligible or ineligible.

D7.9.1.2 A summary of records used to make the donor-eligibility determination.

D7.9.1.3 The name and address of the establishment that made the donor-eligibility determination.

D7.9.1.4 A listing and interpretation of the results of all communicable disease screening and testing performed.

D7.9.1.5 A statement that the communicable disease testing was performed by a laboratory certified under CLIA of 1988, as amended from time to time, has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services, or has met equivalent non-U.S. requirements.

GUIDANCE:

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 standards D7.9.1.1-7.9.1.5. Required is a statement 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 from the Processing Facility for infusion, the product infusion form (see standards D8.2 and B7.2) can be used for this purpose. For products that are distributed to another facility, this information must be included (see standard D12.4 for records to be shared when responsibility for the product is divided). In order for the Processing Facility to provide this information at distribution, it must be obtained from the Clinical or Collection Program (see standard D6.2 and its guidance). When possible, the

Processing Facility should be provided copies of all communicable test result reports as well as the completed donor screening questionnaire along with a final statement attesting to donor eligibility for inclusion in the product processing records. 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.

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 C7.8 and 21 CFR 1251.55). 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 Collection Facility and is transported to another institution for processing, storage, and/or infusion. 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 www.fda.gov/cber/guidelines.htm.

STANDARD:

D7.9.2 In the case of a donor who has been determined to be ineligible based upon screening or testing, and the cellular therapy product has been released by the Processing Facility Medical Director due to urgent medical need, there shall be:

D7.9.2.1 A statement noting the reason(s) for the determination of ineligibility.

D7.9.2.2 Documentation of notification of the physician using the product of the results of all testing and screening.

D7.9.3 Products distributed before completion of donor-eligibility determination shall be accompanied by:

D7.9.3.1 A statement that the donor-eligibility determination has not been completed.

D7.9.3.2 The results of required donor screening or testing that have been completed.

D7.9.3.3 A listing of any required screening or testing that has not yet been completed.

D7.9.3.4 Documentation that the physician using the cellular therapy product was notified that testing or screening was not complete.

D7.9.4 Instructions for use to prevent the introduction, transmission, or spread of communicable diseases shall accompany the product.

GUIDANCE:

Consistent with the GTP regulations, FACT-JACIE Standards allow for products obtained from ineligible 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 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 B6.8.7 also requires that the donor and recipient of a product from an ineligible provide documented informed consent before the product is collected and distributed by the Processing Facility for use.

Products that are needed for infusion before all required donor screening and testing are complete may also be distributed provided that the distribution documents (the product infusion form may be used for this) includes a statement that eligibility determination is not complete, the results of the 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 transplant physician was notified of the incomplete testing or screening. While there is no specific requirement for Processing Facility Medical Director approval in this standard, such approval would be desirable. 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 standard D8.1.2.2).

At the time of distribution, the 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. A "Circular of Information for the Use of Cellular Therapy Products" document (prepared jointly by the American Association of Blood Banks, America's Blood Centers, American Red Cross, American Society for Blood and Marrow Transplantation, International Society of Cellular Therapy, Foundation for the Accreditation of Cellular Therapy and National Marrow Donor Program) contains information that is suitable for this purpose.

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 the standards in section D7.9.

STANDARD:

D7.10 ADDITIONAL DOCUMENTATION AT OR IMMEDIATELY AFTER DISTRIBUTION

D7.10.1 For 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 and that the physician using the product was informed of the results of that determination.

D7.10.2 If required by applicable regulations, the following shall accompany the product:

D7.10.2.1 The statement "Caution: New drug limited by federal law for investigational use only" for products under IND or IDE.

D7.10.2.2 The statement "Rx Only" for licensed products.

GUIDANCE:

The Processing Facility must inform the transplant 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.

Products that are regulated under the FDA 351 regulations must be labeled with the statement "Caution: New drug limited by federal law for investigation use only." Currently HPC, Apheresis products and HPC, Cord Blood from unrelated donors are regulated under an IND held by NMDP. Such products must contain this statement, attached or affixed to the label or accompanying the product. 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.

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 distribution 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, but this may not remain the case much longer. Once licensed products are approved, the inspector should ensure that they are distributed with the required statement on the label or in the accompanying records.

D8 DISTRIBUTION

STANDARD:

D8.1 PROCESSING, TRACKING, AND RELEASE CRITERIA

D8.1.1 The processing and tracking records for each cellular therapy product shall be reviewed, prior to product release/distribution, by the Processing Facility Director or designee for compliance with Standard Operating Procedures and applicable regulations.

D8.1.1.1 Records shall demonstrate traceability from the donor to the recipient and from the recipient to the donor.

D8.1.2 Each cellular therapy product issued for infusion shall meet pre-determined release criteria including donor eligibility prior to issue from the laboratory.

D8.1.2.1 The Processing Facility Medical Director or designee shall give specific authorization for exceptional release when the cellular therapy product does not meet release criteria.

D8.1.2.2 Documentation of agreement of the Processing Facility Medical Director 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 infusion 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 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 products release.

GUIDANCE:

By definition, distribution is the conveyance or shipment (including importation and exportation) of a cellular therapy product that has been determined to meet appropriate release criteria, whether or not such conveyance or shipment is entirely intrastate. 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 (see D7.9 and D7.10), the facility's own SOPs, and with applicable regulations such as GTP. Documentation of specific areas of review must include:

- Donor test results to ensure that all are negative or non-reactive for relevant communicable disease agents.
- Confirmation that testing was performed by a laboratory that meets CLIA requirements or requirements equivalent to CLIA as determined by the CMS.

- 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 must be bi-directional from donor to recipient and from recipient to donor.
- Review of donor medical screening summary records for high-risk behavior and medical evidence of communicable disease.
- Temperature storage records to ensure that the product has been maintained within the prescribed temperature range. This can be done by verifying that the product was stored in monitored equipment and that there are no deviations in the processing record indicating that the device temperature was outside of the designated ranges.
- Review of the entire processing record for completeness, accuracy, and adherence to SOPs.

This review must be documented and the records maintained.

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. 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. While the Processing Facility Director or designee may approve the release of products that meet release criteria, the Processing Facility Medical Director or another suitable designee with the appropriate medical background, must authorize exceptional release. It is left to the Processing Facility to define who the "designee" would be that meets the knowledge requirement for approval/release of a product under exception, and this should be clearly defined in the facility SOP for product approval/release. The processing record of products issued under exceptional release must include documentation of consent from the recipient's physician. 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 Medical Director (or designee) approval and physician notification is present.

It is recommended that the processing record include a checklist or other worksheet to document the review process prior to distribution, including the requirement for Processing Facility Medical Director and/or physician approval for exceptional release.

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. The inspector should look for documentation of the inspection process in the product processing records.

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 Name and 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 supplied the product.

D8.2.2 The distribution record shall include documentation of:

D8.2.2.1 The date and time of receipt.

D8.2.2.2 The identity of the individual who accepted the cellular therapy product.

GUIDANCE:
The inspector should verify the presence of product distribution records in the Processing Facility files for each product that is released for distribution. 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 donor eligibility, if applicable (See standard D7.9.1 & 7.9.2). If the 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 section B7.2.2 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 D7.9 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. The inspector should confirm that identification checks and product receipt are documented in the distribution records.

STANDARD:
D8.3 CIRCULAR OF INFORMATION

D8.3.1 For each type of cellular therapy product, the laboratory shall maintain and distribute or make available to clinical staff a current document 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.

GUIDANCE:
The frequency with which individuals are involved in infusion of a given type of HPC 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. A "Circular of Information For the Use of Cellular Therapy Products" document has been prepared jointly by the American Association of Blood Banks, America's Blood Centers, American Red Cross, American Society for Blood and Marrow Transplantation, International Society of Cellular Therapy, Foundation for the Accreditation of Cellular Therapy and National Marrow Donor Program. This document provides the information listed in D8.3 for virtually all 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: www.factwebsite.org.

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 Processing Facility may wish to issue a ”Circular of Information” with each infusion although this is not required by FACT-JACIE 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 annually and must reflect the current practices in the facility. The inspector should review the current version of the instructions for administration and its availability at the sites of infusion.

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 transportation.

D8.4.2 If the criteria in Sections D8.4.1.1 and D8.4.1.2 have not been met, the Processing Facility shall not accept the product unless the Processing Facility Director or designee gives specific authorization to accept the product for return to inventory after determining the product is acceptable.

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.

GUIDANCE:

The return of any HPC 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 Processing Facility, it should be stressed to the medical staff that this be done as soon after issue as possible. All events surrounding the release and return of the product must be documented in the Processing Facility records including the reason for return. The Processing 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 Processing 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. Both the original and copies of subsequent infusion records must be maintained in the Processing Facility record. Return of products and conditions of re-storage,

reissue or disposal shall be described in an SOP, logically as part of the Processing Facility's SOP for release and exception release SOP (see D5.1.9). 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.

Note that FACT-JACIE Standards now require a procedure for product recall (D5.1.10) 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. 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.

D9 STORAGE

STANDARD:

D9.1 Facilities storing cellular therapy products shall control storage areas to prevent mix-ups, deterioration, contamination, cross-contamination and improper release of products.

D9.2 STORAGE DURATION

D9.2.1 Facilities storing cellular therapy products shall establish policies for the duration and conditions of storage and indications for disposal.

D9.2.1.1 Patients, donors, and associated cell therapy centers should be informed about these policies before the cellular therapy product collection.

D9.2.2 Facilities processing, storing, and/or releasing cellular therapy products for administration shall assign an expiration date and time, as appropriate, for fresh products and for products thawed after cryopreservation.

D9.3 TEMPERATURE

D9.3.1 Storage temperatures shall be defined in the Standard Operating Procedures Manual.

D9.3.2 Cellular therapy products stored in a liquid state 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 the Standard Operating Procedures Manual.

D9.3.3 Cryopreserved products shall be stored within a temperature range, as defined in the Standard Operating Procedures, that is appropriate for the cell product and cryoprotectant solution used.

GUIDANCE:

The Processing Facility must establish a process to ensure that 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. Standards D2.2.1 and D2.4 require 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 fresh, cryopreserved, and thawed cellular therapy products. Products that have been processed and 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., 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 Processing 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 temperature at which products are handled and processed prior to storage. Likewise, transport 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 LN_2 (-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 facility's own experience and must include methods to reduce the risk of contamination or cross contamination (See also standard D9.4.2). 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 shown to be adequate based on the medical literature and/or justified by validation studies have been met. In the EU however, the expiry date must be part of the product information for all tissues and cells.

Donors, recipients and associated transplant centers should be informed of the conditions of storage and storage duration, preferably before product collection. This may be accomplished by informed consent, contractual agreement or other legal means. The inspector should review the facility's established storage criteria for all relevant products and any related contracts or consents.

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 products.

D9.4.2 For products immersed in liquid nitrogen, procedures to minimize the risk of cross-contamination of products shall be employed.

D9.4.3 Facilities storing cellular therapy products shall quarantine each product until completion of the donor eligibility determination, as required by governmental regulations.

D9.4.4 Quarantined cellular therapy products shall be easily distinguishable and stored in a manner that minimizes cross-contamination and inappropriate release.

GUIDANCE:
Evidence has been published demonstrating the possibility of cross-contamination of products stored in the liquid phase of liquid nitrogen with infectious virus. (Reference: 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.). The inspector should review the Processing Facility's program to reduce the likelihood of cross-contamination of containers in liquid phase storage. Such a program may include but may not be limited to the following practices:

- Protective outer coverings over the primary freezing bag
- Prohibition of storage of HPC products from patients and/or donors with positive infectious disease markers or products that have not been tested
- Use of vapor-phase storage
- Use of mechanical freezer storage

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. Infections occurring in patients following the infusion of cryopreserved 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 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, though this could be done, 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. The methods suggested above are effective in minimizing the potential of cross-contamination of products that are stored frozen. Fresh products may more appropriately be stored in a separate area in the Processing Facility while release testing is being performed. Appropriate labeling should be used to distinguish 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. Alternatively a validated electronic release system may be used that prevents the inappropriate release of products. If an electronic system is used for product release, an audit trail that indicates who was responsible for the release must exist. The inspector should review the systems that are in place to distinguish quarantined cellular therapy products and to prevent their inappropriate release.

STANDARD:

D9.5 MONITORING

D9.5.1 Refrigerators and freezers for cellular therapy product storage shall have a system to monitor the temperature continuously and to record the temperature at least every four (4) hours.

D9.5.1.1 For cellular therapy products fully immersed in liquid nitrogen, continuous temperature monitoring is not required.

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 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 If laboratory 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.

D9.6.4 Alarms shall be set to activate at a temperature or level of liquid nitrogen that will allow time to salvage products.

D9.6.5 There shall be written instructions to be followed if the storage device fails. These instructions shall be displayed in the immediate area of the storage device.

D9.6.5.1 A procedure for notifying laboratory personnel shall be placed at each remote alarm location and in the immediate area of the storage device.

D9.6.5.2 In the event of storage device failure, the written instructions shall outline procedures that ensure that cellular therapy products are maintained at safe temperatures. Any corrective actions in order to maintain integrity of the cellular therapy product shall be documented.

D9.6.6 Alarm systems shall be checked periodically for function.

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

GUIDANCE:
It is required that storage temperature be monitored on a continuous basis and that temperatures be recorded at not less than a four hour interval. 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/potency of the product. The Processing Facility should establish critical values that if exceeded require documentation in the facility 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 Processing Facility Director or designee, makes a decision regarding continued storage of the product. As specified elsewhere in these Standards, the Processing Facility must have written procedures specifying actions to be taken in the case of cryopreservation failure. The inspector should review these instructions.

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. 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. This may include instructions on "who to contact," and is particularly applicable in 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. If temperatures fall outside of the established critical ranges, representative 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 HPC 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 D5.1.8). Records of temperatures during storage must be available, with notations made for action taken when temperatures fall outside of the designated range. The inspector should review records of storage device alarm checks of function and triggering at the appropriate limits (temperature, liquid level, etc). For products in the liquid phase of nitrogen storage, 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.

STANDARD:

D9.7 SECURITY

D9.7.1 The storage device shall be located in a secure area and accessible only to authorized personnel.

D9.8 INVENTORY CONTROL

D9.8.1 An inventory control system to identify the location of each product and associated sample aliquots shall be in use.

D9.8.2 The inventory control system records shall include:

D9.8.2.1 Donor name or unique identifier

D9.8.2.2 Recipient name or unique identifier (if known)

D9.8.2.3 Product unique identifier

D9.8.2.4 Product or specimen proper name

D9.8.2.5 Date and time (including time zone if appropriate) of collection

D9.8.2.6 Storage device identifier

D9.8.2.7 Location within the storage device

D9.8.2.8 Date of issue

D9.8.2.9 Disposition

GUIDANCE:

Products for infusion must be in secure locations (storage devices with locks, electromagnetic security capabilities or an enclosed room with door locks) so as to prevent accidental or deliberate tampering

with products or with storage devices that may result in failure to maintain the proper storage temperature.

There must be a mechanism by which 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. This system may be in the form of an electronic database or may consist of log books or other manual systems. The system shall include the elements described in D9.8.2. The inspector should ask for a demonstration of the system including verification that the 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.

D10 RECEIPT AND TRANSPORTATION

STANDARD:

D10.1 Procedures shall be established, maintained, and documented for acceptance, rejection, or quarantine, and transportation of cellular therapy products.

D10.1.1 Each cellular therapy product shall be inspected at receipt to verify the integrity of the container and appropriate labeling, and to evaluate for evidence of microbial contamination.

D10.1.2 There shall be procedures to verify that the cellular therapy product was appropriately transported and that it is accompanied by appropriate documentation and samples.

D10.1.3 There shall be procedures to maintain cellular therapy products in quarantine until they have been determined to meet criteria for release from quarantine.

GUIDANCE:

The Processing Facility must have procedures in place that describe the process of product receipt into the Processing Facility (See D5.1.1) and for product transport (See D5.1.13). The product receipt SOP must minimally describe the criteria for product acceptance, rejection, and quarantine. Documentation at receipt must include the integrity of the primary container and confirmation that the label information meets the requirements specified in Appendix I. There must also be a visual examination of the cellular therapy product for evidence of microbial contamination (excess hemolysis or inappropriate cloudiness, or other unusual appearance). The receipt process must also document that the required accompanying documentation was received (See D6.2 and D7.9) and the presence of product samples. Product samples must be labeled so as to be clearly identified with the donor. In many cases donor screening and test results will have been received into the Processing Facility prior to product receipt. EU requirements for documents that should be supplied to the Processing Facility that are not addressed by FACT-JACIE Standards 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, and where relevant, the date and time of donor death. 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 should be in the form of a collection report. For EU inspections, the presence of such a report with the required information in the accompanying documents at product receipt should be confirmed.

As indicated in the guidance for standard D9.4, a process to store products in quarantine until they have been determined to meet all predetermined release criteria must be in place. The inspector should

review documentation of product receipt into the Processing Facility to ensure compliance with the facility's SOPs and these Standards.

STANDARD:

D10.2 Procedures for transportation of non-frozen and/or cryopreserved products shall be designed to protect the integrity of the product and the health and safety of individuals in the immediate area.

D10.2.1 The primary product container for non-frozen products shall be placed in a secondary plastic bag and sealed to prevent leakage.

D10.3 All cryopreserved or non-frozen products that require a temperature-controlled environment and that are transported within a facility over an extended time shall be transported in a container validated to maintain the appropriate temperature range.

D10.4 All products that leave the facility shall be transported in an outer shipping container.

D10.4.1 Shipping conditions shall be established and maintained to preserve the integrity and safety of cellular therapy products during transport.

D10.4.2 The outer shipping container shall conform to the applicable regulations regarding the mode of transport.

D10.4.3 The outer shipping container shall be made of material adequate to withstand leakage of contents, shocks, pressure changes, and other conditions incident to ordinary handling in transportation.

D10.4.4 The shipping container shall be validated to be of appropriate design and construction to preserve the integrity of the cellular therapy product and to protect it from contamination during transport.

D10.4.5 During transport, the product temperature shall be maintained at the storage temperature specified by the Processing Facility.

D10.4.5.1 The shipping facility shall transport products in a shipper validated to maintain appropriate temperature.

D10.4.5.2 The temperature of shippers containing cryopreserved products shall be continuously monitored during transportation.

D10.4.5.3 The shipping facility shall maintain a record of the temperature during transport.

D10.4.5.4 The receiving facility shall verify and record the acceptability (i.e. integrity, appearance, etc.) of the product.

D10.4.5.5 The receiving facility shall document the temperature of the shipper upon arrival. For cryopreserved products, processing records shall include documentation of the container temperature during transport.

GUIDANCE:

The Processing Facility shall have written policies and procedures for the transportation of cellular therapy products that includes internal sites, such as from the Collection Facility to the Processing

Facility and at distribution from the Processing Facility to internal sites or to facilities external to the supported Clinical Program. These procedures must ensure maintenance of optimal temperature during transport. The product must be packaged to protect it from potential harm during transit and to prevent exposure of individuals involved in its transport to potentially infectious agents. It is strongly recommended that when heat sealers are used on the primary container, a minimum of three (3) seals be applied and that secondary containers are also securely sealed. Human tissue, regardless of infectious disease testing, must be considered potentially infectious. For fresh 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 transport. The product temperature during transit is dependent upon a number of variables, including: the transport time, the anticoagulants used, and the requirement for further processing. The ideal transport temperature may range from 1-24°C. There must be a prospective agreement among the collecting, processing, and receiving facilities regarding transport conditions. Most products should not be transported at temperatures above 24°C. Products not previously cryopreserved should never be allowed to cool to temperatures below freezing. Transport between facilities that are not adjacent to each other, must always use an outer shipping container that protects the product from adverse conditions encountered during transport (air pressure changes, rough handling, etc), and has been validated to maintain the agreed upon transport temperature. For products transported between sites of a single program, the distance between the collection site and the Processing Facility varies widely. For situations where transport from the collection site to the Processing Facility requires only minutes, as long as the product is transported safely, a controlled temperature environment may not be required. 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 validated outer shipping container. The inspector must determine if the transport procedures in use within the Program are adequate for the conditions.

For non-cryopreserved products, a thermally insulated shipping container should be used with cold packs added as necessary to maintain the required temperature. For cryopreserved products, a LN_2 vapor shipper (dry shipper) should be utilized. The vapor shipper must contain adequate absorbed LN_2 to maintain the temperature at least 48 hours beyond the expected time of arrival at the receiving facility. The temperature of shippers containing cryopreserved products must be continuously monitored and that record must be maintained by the shipping facility. Documentation of the container temperature at receipt and during transport is also required for the processing records of the receiving facility. Continuous monitoring that creates a record can only be performed using 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. Since cryopreserved product primary containers are susceptible to breakage, they must be packaged so to minimize movement during transit and the acceptability of the product verified at receipt. Validation and periodic quality control must be performed on all shippers and data loggers.

Containers for transport of products that leave the facility or are transported on public roads must be made of durable material and insulation that will withstand leakage of contents, shocks, pressure changes, and temperature extremes. The containers must be validated prior to use to ensure proper performance for all expected transportation 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.

Transport 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 must include all documentation of donor eligibility as defined in 21 CFR 1271.55 and above (Standards C7.8). Labeling requirements are defined in Standards, Appendix III.

The inspector should review receipt records of both fresh and cryopreserved products shipped and received by the Processing Facility for adherence to these Standards.

STANDARD:

D10.4.6 The outer shipping container shall be labeled as defined in the Cellular Therapy Product Shipping Labels Table in Appendix II.

D10.4.7 There shall also be a label inside the shipping container that includes all the information required on the outer shipping container, in conformity with the Cellular Therapy Product Labeling Table in Appendix I and the Cellular Therapy Product Shipping Labels Table in Appendix II.

D10.4.8 The shipping container shall be labeled in accordance with applicable regulations regarding the cryogenic material used and the transportation of biologic materials.

GUIDANCE:

Labeling that must be affixed to shipping container is specified in Appendix II and includes:

- Distribution Date (Note EU regulations also require the time at the start of transport)
- Statement “Do Not X-Ray”
- Statement “Medical Specimen, Handle With Care”
- Shipper handling instructions (Note EU regulations require specifications of the conditions of transport relevant to the quality and safety of the tissues and cells)
- Shipping facility name, street address and phone number
- Receiving facility name, street address, and phone number
- Identity of person or position responsible for receipt of the shipment

The inner shipping label must contain this information together with the appropriate biohazard and warning statements. Biohazard and warning statements should not be on the exterior of the shipping container due to requirements by some carriers.

Information regarding the intended destination and responsible individual at that center is required for contact in the event of delay or emergency or in case there are delays during transit or questions about the product arise after it reaches its destination. Having this information attached to the shipper 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 label; however, unique identifiers are appropriate. The inspector should review transportation records and should observe shipping containers to ensure that the elements in this section are met and documented. The Processing Facility personnel are responsible for verifying the labeling requirements of any courier services utilized.

STANDARD:

D10.5 Method of Transport

D10.5.1 The transit time should be minimized.

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 transport in an emergency.

D10.5.4 The 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.

D10.6 Transport Records

D10.6.1 Transport records shall permit tracing of the cellular therapy product from one facility to another.

D10.6.2 Transport records shall include:

D10.6.2.1 Date and time product was shipped

D10.6.2.2 Date and time product was received

D10.6.2.3 Shipping facility

D10.6.2.4 Receiving facility

D10.6.2.5 Personnel responsible for shipping and receiving product

D10.6.2.6 Identity of courier

D10.6.2.7 Any delay or problems incurred during transport

GUIDANCE:
If a patient has undergone high-dose marrow ablative treatment in preparation for transplant, the 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 collection center to the receiving facility. Alternative transportation plans in case the primary arrangement fails are required. Transport 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.

Transport records must be complete to allow tracking of the product from one facility to another. Transport records must document the identity of all responsible personnel including the courier and any delays or problems occurring during product transportation.

The inspector should ask to review transportation records for products transported within the institution and for those transported between facilities for compliance with this section of the Standards.

D11 DISPOSAL

STANDARD:
D11.1 There shall be written policies for disposal of cellular therapy products.

D11.2 There shall be written documentation of patient death or no further need for the product before any product is discarded.

D11.3 Prior to collection, there should be a written agreement between the storage facility and the donor or donor's legal representative, or the patient or designated recipient, as appropriate, defining the length of storage and the circumstances for disposal or transfer of cellular therapy products.

D11.3.1 If the patient or designated recipient is still alive at the time of disposal specified by the written agreement, the patient shall be offered the opportunity to transfer the product to another facility.

D11.3.2 If there is no pre-existing agreement describing conditions for product storage and/or discard, the storage facility shall:

D11.3.2.1 Communicate with the designated recipient's physician about continuing need for storage of the product.

D11.3.2.2 Make a documented effort to notify the patient or designated recipient about product disposition or disposal.

D11.3.3 Disposal of cellular therapy products obtained through donor registries shall adhere to conditions mutually agreed upon by the storing facility and the donor registry.

D11.4 The Processing Facility Medical Director, in consultation with the recipient's physician, shall approve of the product discard, disposition, or method of disposal.

D11.5 The method of disposal and decontamination shall meet governmental regulations for disposal of biohazardous materials and/or medical waste.

D11.6 The records for discarded products shall indicate the product was discarded, date of discard, and disposition of product or method of disposal.

GUIDANCE:

The control of the disposal of cellular therapy products must be clearly defined to protect both the patient 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. FACT strongly advises that SOPs for disposal and consents for collection be reviewed by the institution's legal advisors, since the ownership of products vary depending on whether the product is autologous or allogeneic, and can also vary between nations, states, provinces, or other governmental unit that regulates the storage facility.

The most common reasons for disposal are the following:

1. Death of the patient: Death of the patient, identification of products for the patient, and notification of the patients responsible physician must be documented by the storage facility before the product can be discarded.
2. No further need for the product: Under certain circumstances, the physician responsible for the patient may determine there is no further need for the product. If the patient is alive at the time, the facility must offer the patient 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.

3. 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 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 laboratory procedures are not in contradiction with consent forms signed at the time of collection. The Medical Director of the storage facility must show that (s)he consulted with the recipient 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 storage facility Medical Director and recipient's physician.

One of the biggest problems faced by older programs is the disposition of 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 patient or family likewise is a decision left to the individual center. The rights of both the donor (whether related or unrelated) should be protected according to local laws and the standards of donor registries

Products derived from human tissue are considered to be a potential biohazard and adherence to universal precautions is required during the disposal process. 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. 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 products that have been disposed under these Standards, and should be able to track all steps of notification of product discard, method of destruction or transfer, and documentation in patient records of action.

D12 RECORDS

STANDARD:

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 product prior to distribution and for follow-up evaluation or investigation.

D12.1.1.1 The records management system shall facilitate tracking of the product from the donor to the recipient or final disposition and from the recipient, or final disposition, to the donor.

D12.1.1.2 For cellular therapy products that are to be shipped for use at another institution, the consignee shall be informed in writing, at or before the time of distribution of the product, of the tracking system and of the requirement for tracking the product.

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 among the collection, processing, and transplant facilities, and their patients 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 governmental laws and regulations.

D12.1.4 Records shall be made concurrently with each step of the processing, testing, cryopreservation, storage, and infusion or disposal/ disposition/distribution of each product in such a way that all steps may be accurately traced.

D12.1.4.1 Records shall identify the person immediately responsible for each significant step, including dates and times of various steps, where appropriate.

D12.1.4.2 Records shall show the test results and the interpretation of each result, where appropriate.

D12.1.5 Records shall be maintained in one or more of the following ways: electronically, as original paper records, or as true copies.

D12.1.5.1 Equipment to make the records available and legible shall be readily available.

D12.1.5.2 For electronic records Section D12.2 applies.

GUIDANCE:
Each Processing Facility has the flexibility to develop individualized systems of organizing and maintaining records as long as certain objectives are achieved. The record keeping system must be documented and should include, at least:

- 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 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. However, it is recommended that recent records be kept on-site and archived records be readily accessible within a reasonable time frame. The methods for filing and transfer of records to archival storage should be specified in the SOP manual. Records may be maintained electronically, as original paper records, as photocopies, 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. The Processing Facility must make provisions for all records to be maintained for the required period of time in the event that the Processing Facility ceases

operation. Records that allow the tracking of a product from the donor to final disposition and from the recipient to the donor must be maintained even when products are transferred to another facility.

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 U.S. HIPAA regulations or equivalent non-U.S. laws or regulations on confidentiality and data protection. In Europe, the comparable law or regulation is EC 95/46 Directive. This 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 inspector should be alert to breaches in policy that potentially compromise patient or donor confidentiality. Examples 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. The Processing Facility must have SOPs describing the maintenance of donor and recipient confidentiality (See D5.1.31).

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. If research records are stored independently of patient records, the same considerations regarding confidentiality apply. The sponsor of the research, Institutional Review Board, and/or governmental authorities may place specific requirements for long-term maintenance of research records. 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.

Since potency and efficacy may be affected by the competency of the individual(s) performing the processing, testing, cryopreservation, storage, infusion, or disposal of a product, it is critical that the responsible individual(s) be identified for each significant step. This is most easily accomplished by including a place for initials or other identification on relevant worksheets and forms. The inspector should examine paperwork to determine if adequate records are maintained that identify the responsible individual(s) for all significant steps of processing. Likewise, retention of records that identify the manufacturers and lot numbers of all reagents and supplies used for processing is critical for tracking purposes in the event of a problem, recall, or adverse event.

STANDARD:

D12.2 ELECTRONIC RECORDS

D12.2.1 If a computer record-keeping system is used, there shall be a system to ensure the authenticity, integrity, and confidentiality of all records.

D12.2.2 There shall be protection of the records to enable their accurate and ready retrieval throughout the period of record retention.

D12.2.3 There shall be a back-up or alternative system for all electronic records that ensures continuous operation in the event that primary electronic data are not available. The alternative system shall be tested periodically.

D12.2.4 There shall be written procedures for record entry, verification, and revision. A system shall be established for review of data before final acceptance.

D12.2.4.1 The Quality Management Program shall include an assessment of electronic functions to ensure that errors and problems are reported and resolved.

D12.2.5 There shall be a system whereby access to the electronic records is limited to authorized individuals.

D12.2.6 There shall be the ability to generate true copies of the records, in both paper and computer format, suitable for inspection and review.

D12.2.7 When an electronic system is used, there shall be validated procedures for and documentation of:

D12.2.7.1 Systems development

D12.2.7.2 Numerical designation of system versions, if applicable

D12.2.7.3 Prospective validation of system, including hardware, software, and databases

D12.2.7.4 Installation of the system

D12.2.7.5 Training and continuing competency of personnel in systems use

D12.2.7.6 Monitoring of data integrity

D12.2.7.7 Back-up of the electronic records system on a regular schedule

D12.2.7.8 System maintenance and operations

D12.2.8 All system modifications shall be authorized, documented, and validated prior to implementation.

D12.2.9 The electronic system shall ensure that all donor, product, and patient identifiers are unique.

GUIDANCE:
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. For example, an electronic record of the location of a product in LN2 storage is printed for the processing chart and the information is verified by signature or initial. 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. 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 Processing 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 product and/or the integrity of a record. For example, if a computerized system (word processor) is used to generate SOPs, validation is not required since the quality and safety of a 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.

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. Under these circumstances, the inspector should refer to the FDA document *21 CFR Part 11; Electronic Records; Electronic Signatures-Scope and Application* which is available at (http:/www.fda.gov/cder/guidance/5667fnl.pdf) for guidance to assess the validation procedures. Validation procedures under these circumstances are extensive and include such things as:

- Extensive 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, 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
- Verification that the source of data for entry is predefined and consists of original documents whenever possible
- 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 Standard Operating Procedures 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

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

STANDARD:

D12.3 RECORDS TO BE MAINTAINED

D12.3.1 Processing Facility records related to quality control, personnel training or competency, facility maintenance, facility management, or other general facility issues shall be retained for at least 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. Not all records need be immediately available.

D12.3.2 All records related directly to the processing, testing, storage, or release of cellular products shall be maintained for ten (10) years after their creation. The records pertaining to a cellular product shall be maintained at least ten (10) years after the date of its administration, or if the date of administration is not known, then at least ten (10) years after the date of the cellular products distribution, disposition, or expiration, whichever is latest, or according to applicable laws and regulations or institutional policy, whichever requires the longest maintenance period. The following records shall be maintained:

D12.3.2.1 Processing records

D12.3.2.2 Compatibility test records

D12.3.2.3 Cryopreservation records

D12.3.2.4 Distribution records

D12.3.2.5 Records of errors, accidents, adverse events, adverse reactions, and complaints.

D12.3.2.6 All quality management records.

GUIDANCE:

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 in a reasonable time frame, but need not be immediately available within the Processing Facility.

Records that are to be maintained minimally 10 years after their creation include:

- QC records, including all of the items referred to in standard D.4 (Quality Management) including: validation and qualification studies, equipment maintenance reports, the results of audits, errors, accidents and adverse reactions reports, and outcome analysis.

- Personnel training and competency records as detailed in standard D4.6, including job qualification records, records of orientation, initial training, continuing education, and yearly competency assessments

- Facility maintenance, management, or other general facility issues include all of the items referred to in standard D2 including: 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; cleaning schedules; personnel responsible for cleaning and documentation of additional training if required; sterilization records; disposition of supplies and reagents; safety training for biological,

chemical and radiation exposure and/or disposal; 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 include management issues related to facility maintenance including 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 entire institution of which the Processing Facility is a part. These may include: disaster plans; fire response and safety; biological, chemical and radiation disposal policies; and HIPAA confidentiality requirements.

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. In European Union Member States, donor records required for full traceability must be maintained for a period of 30 years. Specific records to be maintained are specified in D12.3.2.1 through D12.3.2.6 and include records of reagents, supplies, and equipment utilized in processing or storing that product. Transmission of infectious disease agent, adverse event in the recipient and/or product recall are events that generally result in an investigation necessitating tracking and tracing. EU regulations on record retention relating to cellular therapy products stored or distributed by the Processing Facility specifically require that 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 processing records.

The inspector should look for evidence of 10-year retention of representative records from each of these categories, including some older and some more recent documents. For example, each Processing Facility should maintain a comprehensive list of all relevant faculty and support staff associated with that facility for the immediate previous 10-year period. The inspector may ask to review the personnel list and then ask to see dated training or competency records for a specific individual. Likewise, the inspector may ask to see the original records of validation of the controlled rate freezers, shipping containers, or cryopreservation technique, assuming the facility is less than 10 years old. It should be acknowledged that the 10-year requirement for record retention exceeds the lifespan of the FACT-JACIE Standards. This should be taken into account during the inspection and the Processing Facility should only be responsible for compliance with this standard from the time of its initial FACT-JACIE accreditation.

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 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 product.

D12.4.3 There shall be a system to allow the Processing Facility access to information that tracks all manufacturing steps performed by other facilities. This tracking system shall comply with D4.12.

D12.4.4 The Processing Facility shall furnish to the facility of final disposition a copy of all records relating to the collection and processing procedures performed in so far as they concern the safety, purity, and potency of the product involved.

GUIDANCE:
In the event that two or more facilities participate in the collection, processing, or transplantation of a 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(s) need not be duplicated for the Processing Facility record. However, the Processing Facility record should allow tracing/tracking of relevant information to the correct source. For example, the Processing Facility may manufacture products for multiple transplant programs. The Processing 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 reagents lot numbers used for steps performed at the collection or transplant facilities. The Processing Facility should verify that such relevant and appropriate records will be maintained by the facility that performs the work. Records of donor eligibility screening and testing must be provided to the Processing Facility as specified in D7.9. 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/tracing from a donor to a recipient and vice versa. The inspector should determine if divided responsibility occurs regarding any aspect of the transplant process, and ask to review a relevant patient file to confirm that an appropriate mechanism is in place to track the process from beginning to end.

Donor and patient 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 National Marrow Donor Program 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 Processing Facility to furnish to all other facilities involved in the collection and/or infusion of the product, any data so far as it concerns the safety, purity, and potency of the product involved. The inspector should review the applicable SOPs regarding dissemination of Processing Facility data and verify that the process is in place.

APPENDICES

CELLULAR THERAPY PRODUCT LABELING

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

Element	Partial label	Label at completion of collection	Label at completion of processing	Label at distribution	Inner shipping container label
Unique numeric or alphanumeric identifier	AF	AF	AF	AF	
Proper name of product	AF	AF	AF	AF	
Product modifiers	AF		AF	AF	
Recipient name and identifier	AF (If applicable)	AT (If applicable)	AT (If applicable)	AT	
Identity and address of collection facility or donor registry		AT	AT	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		AT	AT	AT	
Biohazard and/or Warning Labels (as applicable) see D7.5 and Appendix III.		AT	AT	AT	AF
If applicable: Statement “Not evaluated For Infectious Substances” Statement “Warning: Advise Patient of Communicable Disease Risks” Statement “Warning: Reactive Test Results for [name of disease agent or disease]”		AT AT AT	AT AT AT	AT AT AT	AF
Identity and address of processing and distribution facility(s)			AT	AT	
Statement “Do Not Irradiate”			AT	AF	
Expiration Date (if applicable)			AC	AT	
Expiration Time (if applicable)			AC	AT	
ABO and Rh of donor (if applicable)			AC	AT	
RBC compatibility testing results (if applicable)				AT	
Statement "Properly Identify Intended Recipient and Product"				AT	
Statement indicating that leukoreduction filters should not be used.				AF	
Statement "For Autologous Use Only" (if applicable) OR Statement "For Use By Intended Recipient Only" (if for allogeneic recipient)		AT	AT	AT AT	
Statement “For Nonclinical Use Only” (if applicable)				AT	
Date of distribution				AC	

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

APPENDIX II

CELLULAR THERAPY PRODUCT SHIPPING LABELS

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

Element	Inner & outer shipping container label
Date of distribution	AF
Statement "Do Not X-Ray"	AF
Statements "Medical Specimen", "Handle with Care"	AF
Shipper handling instructions	AF
Shipping facility name, street address and phone number	AF
Receiving facility name, street address, and phone number	AF
Identity of person or position responsible for receipt of the shipment	AF

AF=Affix

Modified table from the *Circular of Information for the Use of Cellular Therapy Products*, AABB et al. July 2005.

Modified Circular of Information Biohazard and Warning Labels

		Title 21 CFR Citation [F]	Status: All Donor Screening and Testing Completed	Status: Abnormal Results of Donor Screening	Status: Abnormal Results of Donor Testing	Status: Donor is resident in country on USDA [E] BSE list OR Testing performed in non-CLIA-certified laboratory.	Status: Urgent Medical Need	Product Labels: Biohazard Legend [per 21 CFR 1271.3(h)]	Product Labels: For Autologous Use Only	Product Labels: Not Evaluated for Infectious Substances	Product Labels: WARNING: Advise patient of communicable disease risks	Product Labels: WARNING: Reactive test results for (name of disease agent or disease)
Donor Eligibility Determination Required [21 CFR 1271.45(b)]												
1	Allogeneic donors with incomplete donor eligibility determination [A,B]	1271.60	No	No	No		Yes			X	X	
2	Allogeneic donors found ineligible											
	A first-degree or second-degree blood relative [C]	1271.65(b) 1.i	Yes	No/Yes	Yes		NA	X			X	X
	A first-degree or second-degree blood relative [C]	1271.65(b) 1.i	Yes	Yes	No		NA	X			X	
	Unrelated donor	1271.65(b) 1.ii	Yes	No/Yes	Yes		Yes	X			X	X
	Unrelated donor	1271.65(b) 1.ii	Yes	Yes	No		Yes	X			X	
	Unrelated donor (USA Regulation [G])		Yes	No	No	Yes	Yes	X			X	
Donor Eligibility Determination Not Required [21 CFR 1271.90(a)]												
3	Autologous donors [D]	1271.90(a)(b)										
	Autologous donor	1271.90(a)(1)(2)	No	No	No				X	X		
	Autologous donor	1271.90(b)(1)(3)	Yes	No/Yes	Yes			X	X			X
	Autologous donor	1271.90(b)(1)(3)	Yes	Yes	No			X	X			

A. The donor eligibility must be finalized during or after the use of the cellular therapy product. The results must be communicated to the treating physician [21 CFR 1271.60 (b)4].
B. Abnormal results of any screening or testing requires labeling as in item 2 in this table (21 CFR 1271.65 applies).
C. Notification of the recipient's and donor's physicians of abnormal screening and/or testing results is required.
D. Any abnormal donor screening or testing results (even though neither screening nor testing is mandated for this group of donors) require appropriate labeling [21 CFR 1271.90 (b)].
E. USDA – United States Department of Agriculture.
F. USA Federal Register, Code of Federal Regulations, Part 1271, Human Cells, Tissues, and Cellular Based Products, Revised January 1, 2004.
G. Applies to any cord blood unit collected, processed, stored, transported or transplanted in the US.

Transplant Essential Data
First Report: 100 Days Post Transplant
Disease Classification Sheet 1

PATIENT IDENTIFICATION
Hospital Unique Patient Number: _____

CENTER IDENTIFICATION
Center Identification Code:
IBMTR/ABMTR _____

ACUTE LEUKEMIAS

Classification:

Acute Myelogenous Leukemia (AML)
- ❑ M0
- ❑ M1
- ❑ M2
- ❑ M3
- ❑ M4
- ❑ M5
- ❑ M6
- ❑ M7
- ❑ AML NOS
- ❑ Transformed from MDS — *Complete entire MDS Section on Disease Classification Sheet 2 and remainder of AML Section, except status at transplantation*
  - FAB classification: M____
- ❑ Other AML, specify:_____

Acute Lymphoblastic Leukemia (ALL)
- ❑ ALL B-lineage
- ❑ ALL T-lineage
- ❑ Mature B cell (L3)
- ❑ T-cell granular lymphocytic leukemia
- ❑ Aggressive NK-cell leukemia
- ❑ Adult T-cell lymphoma/leukemia (HTLV1+)
- ❑ ALL NOS
- ❑ Other ALL, specify:_____

Other Acute Leukemias
- ❑ Acute undifferentiated
- ❑ Acute biphenotypic
- ❑ Acute mast cell leukemia
- ❑ Other acute leukemia, specify:_____

Was Gleevec (STI571, imatinib mesylate) given for pretransplant therapy? ❑Yes ❑No ❑Unknown
Was AML caused by prior exposure to therapeutic drugs or radiation? ❑Yes ❑No ❑Unknown

Status at Transplantation:
- ❑ Untreated
- ❑ Primary Induction Failure (PIF)
- ❑ CR — Number ❑1st ❑2nd ❑3rd or higher
- ❑ Rel — Number ❑1st ❑2nd ❑3rd or higher

For Complete Remission

Y	N	Unk	
❑	❑	❑	Cytogenetic remission
❑	❑	❑	Molecular remission

CHRONIC MYELOGENOUS LEUKEMIA (CML)

Classification:
- ❑ CML, Ph+
- ❑ CML, Ph-
- ❑ CML, NOS

Prior treatment (check all that apply):
- ❑ Interferon
- ❑ Hydroxyurea (HU)
- ❑ Gleevec (STI571, imatinib mesylate)
- ❑ Other, specify:_____

Status at Transplantation:

Phase
- ❑ Chronic phase
- ❑ Accelerated phase
- ❑ Blast crisis

Number
- ❑ 1st
- ❑ 2nd
- ❑ 3rd or higher

For Chronic Phase Only *(check all that apply)*
- Hematological remission: ❑Yes ❑No, stable phase
- Cytogenetic remission: ❑Complete ❑Partial ❑Cytogenetics unknown
- Molecular (bcr/abl): ❑Present ❑Absent ❑bcr/abl unknown
- Other: _____

OTHER LEUKEMIAS

Classification:
- ❑ Chronic Lymphocytic Leukemia (CLL), B-cell/ small lymphocytic lymphoma
- ❑ CLL, T-cell
- ❑ CLL, NOS
- ❑ Prolymphocytic Leukemia
  - ❑ B-cell
  - ❑ T-cell
- ❑ Hairy Cell Leukemia
- ❑ Other leukemia, specify:_____

Status at Transplantation:
- ❑ Untreated
- ❑ CR
- ❑ PR
- ❑ No response/stable
- ❑ Progression

CR=complete remission, PR=partial remission, Rel=relapse, CP=chronic phase, AP=accelerated phase, BP=blast phase

Transplant Essential Data
First Report: 100 Days Post Transplant
Disease Classification Sheet 2

PATIENT IDENTIFICATION
Hospital Unique Patient Number: _____

CENTER IDENTIFICATION
Center Identification Code:
IBMTR/ABMTR _____

MYELODYSPLASTIC OR MYELOPROLIFERATIVE SYNDROMES

Classification:

Myelodysplastic Syndromes (MDS)*

At diagnosis	At transplantation
☐	☐ RA
☐	☐ RARS
☐	☐ RAEB
☐	☐ RAEB-t
	☐ AML
☐	☐ MDS NOS
☐	☐ Other, specify: _____

Myeloproliferative Syndromes (MPS)

At diagnosis	At transplantation
☐	☐ Polycythemia vera
☐	☐ Essential or primary thrombocythemia
☐	☐ Myelofibrosis with myeloid metaplasia
☐	☐ Acute myelofibrosis or myelosclerosis
☐	☐ MPS, NOS
☐	☐ Other MFS/MPS, specify: _____

Other

At diagnosis	At transplantation
☐	☐ Chronic myelomonocytic leukaemia (CMMol, CMML)
☐	☐ Juvenile myelomonocytic leukaemia (JMML, JCML, JCMML)

Status at Transplantation:

- ☐ Untreated (Supportive care only)
- ☐ Treatment without intent to achieve CR
- ☐ Treatment with intent to achieve a CR – CR not achieved
- ☐ Treatment with intent to achieve a CR – CR achieved and sustained
- ☐ Relapse after CR

Number
☐ 1st
☐ 2nd
☐ 3rd or higher

** If transformed to acute leukemia report on Disease Classification Sheet 1*

ANEMIA/HEMOGLOBINOPATHY

Classification:

- ☐ Acquired Severe Aplastic Anemia (SAA), Idiopathic
- ☐ Acquired SAA, secondary to hepatitis
- ☐ Acquired SAA, secondary to toxin/other drug
- ☐ Amegakaryocytosis acquired (not congenital)
- ☐ Acquired Pure Red Cell Aplasia (PRCA) (not congenital)
- ☐ Schwachmann-Diamond
- ☐ Other acquired cytopenic syndrome, specify: _____
- ☐ Fanconi anemia
- ☐ Diamond-Blackfan anemia (congenital PRCA)
- ☐ Other constitutional anemia, specify: _____
- ☐ Thalassemia NOS
- ☐ Sickle cell disease
- ☐ Other hemoglobinopathy, specify: _____
- ☐ Paroxysmal nocturnal hemoglobinuria (PNH)

PLATELET DISORDERS

Classification:

- ☐ Congenital amegakaryocytosis/congenital thrombocytopenia
- ☐ Glanzmann thrombasthenia
- ☐ Other inherited platelet abnormalities, specify: _____

HISTIOCYTIC DISORDERS

Classification:

- ☐ Histiocytic disorders, NOS
- ☐ Familial erythro/hemophagocytic lymphohistiocytosis (FELH)
- ☐ Langerhans Cell Histiocytosis (Histiocytosis-X)
- ☐ Hemophagocytosis (reactive or viral associated)
- ☐ Malignant histiocytosis
- ☐ Other histiocytic disorder, specify: _____

CR=complete remission

Transplant Essential Data
First Report: 100 Days Post Transplant
Disease Classification Sheet 3

PATIENT IDENTIFICATION
Hospital Unique Patient Number: _____

CENTER IDENTIFICATION
Center Identification Code:
IBMTR/ABMTR _____

LYMPHOMAS

Classification:

☐ Hodgkin Disease

Non-Hodgkin's Lymphoma

B-cell Neoplasms
- ☐ Precursor B-lymphoblastic leukemia/ lymphoma (precursor B-cell acute lymphoblastic leukemia)
- ☐ Lymphoplasmacytic lymphoma
- ☐ Splenic marginal zone B-cell lymphoma
- ☐ Extranodal marginal zone B-cell lymphoma of MALT type
- ☐ Nodal marginal zone B-cell lymphoma (+/– monocytoid B cells)
- ☐ Follicular lymphoma
  - ☐ Grade I
  - ☐ Grade II
  - ☐ Grade III
  - ☐ Unknown
- ☐ Mantle cell lymphoma
- ☐ Diffuse large B-cell lymphoma
- ☐ Burkitt's lymphoma/Burkitt cell leukemia
- ☐ Other B-cell lymphoma, specify:_____

T-cell and NK-cell Neoplasms
- ☐ Precursor T-lymphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia)
- ☐ Extranodal NK/T-cell lymphoma, nasal type
- ☐ Enteropathy-type T-cell lymphoma
- ☐ Hepatosplenic gamma-delta T-cell lymphoma
- ☐ Subcutaneous panniculitis-like T-cell lymphoma
- ☐ Mycosis fungoides/Sezary syndrome
- ☐ Anaplastic large-cell lymphoma, T/null cell, primary cutaneous type
- ☐ Peripheral T-cell lymphoma, NOS
- ☐ Angioimmunoblastic T-cell lymphoma
- ☐ Anaplastic large-cell lymphoma, T/null cell, primary systemic type
- ☐ Other T/NK cell lymphoma, specify:_____

Status at Transplantation:
- ☐ Untreated
- ☐ Primary refractory (less than partial response to initial therapy)
- ☐ CR
  - ☐ CR confirmed
  - ☐ CR unconfirmed (CRU)
- ☐ 1st partial response (PR1)
- ☐ Rel

Number
- ☐ 1st
- ☐ 2nd
- ☐ 3rd or higher

Sensitivity to Chemotherapy:
(within 6 months prior to transplantation)
- ☐ Sensitive
- ☐ Resistant
- ☐ Untreated
- ☐ Unknown

* CRU – complete response with persistent scan abnormalities of unknown significance

PLASMA CELL DISORDERS

Classification:
- ☐ Multiple myeloma-IgG
- ☐ Multiple myeloma-IgA
- ☐ Multiple myeloma-IgD
- ☐ Multiple myeloma-IgE
- ☐ Multiple myeloma-light chain only
- ☐ Multiple myeloma-non-secretory
- ☐ Plasma cell leukemia
- ☐ Solitary plasmacytoma (no evidence of myeloma)
- ☐ Waldenstrom macroglobulinemia (IgM)
- ☐ Primary Amyloidosis
- ☐ Other Plasma Cell Disorder, specify: _____

SALMON & DURIE
Stage at Diagnosis
(Multiple Myeloma only)
- ☐ 1 and ☐ A
- ☐ 2 ☐ B
- ☐ 3

Status at Transplantation:
- ☐ Untreated
- ☐ CR
- ☐ PR
- ☐ MR
- ☐ Progression/Relapse
- ☐ No response/Stable disease

Number
- ☐ 1st
- ☐ 2nd
- ☐ 3rd or higher

CR=complete remission, PR=partial remission, Rel=relapse, MR=minimal response

Transplant Essential Data
First Report: 100 Days Post Transplant
Disease Classification Sheet 4

PATIENT IDENTIFICATION
Hospital Unique Patient Number: _____

CENTER IDENTIFICATION
Center Identification Code:
IBMTR/ABMTR _____

BREAST CANCER

Classification:

Breast Cancer
- ☐ Inflammatory
- ☐ Non-inflammatory

Stage at Diagnosis
- ☐ 0
- ☐ I
- ☐ II
- ☐ III
- ☐ Inflammatory, no distant metastases
- ☐ Metastatic

Status at Transplantation:

- ☐ Adjuvant (Stage II, III only)
- ☐ Untreated (upfront)
- ☐ Primary refractory
- ☐ Complete remission (CR)
  - ☐ CR confirmed
  - ☐ CR unconfirmed (CRU)
- ☐ 1st partial response (PR1)
- ☐ Relapse
  - ☐ Local
  - ☐ Metastatic

Number
(complete only for CR or relapse)
- ☐ 1st
- ☐ 2nd
- ☐ 3rd or higher

Sensitivity to Chemotherapy
(complete only for relapse)
- ☐ Sensitive
- ☐ Resistant
- ☐ Untreated
- ☐ Unknown

* CRU – complete response with persistent scan abnormalities of unknown significance

OTHER MALIGNANCIES

Classification:

- ☐ Head and neck
- ☐ Lung cancer, small cell
- ☐ Lung cancer, non-small cell
- ☐ Lung cancer, NOS
- ☐ Thymoma
- ☐ Gastric
- ☐ Colorectal
- ☐ Pancreas
- ☐ Hepatobiliary
- ☐ Kidney and urinary tract
- ☐ Wilm tumor
- ☐ Prostate
- ☐ Testicular
- ☐ External genitalia
- ☐ Cervical
- ☐ Uterus
- ☐ Ewing sarcoma
- ☐ Ovary
- ☐ Vagina
- ☐ Germ cell tumor, extragonadal
- ☐ Sarcoma NOS
- ☐ Soft tissue sarcoma (include sarcoma PNET)
- ☐ Bone sarcoma (excluding Ewing sarcoma) (include sarcoma PNET)
- ☐ Rhabdomyosarcoma
- ☐ Leiomyosarcoma
- ☐ Liposarcoma
- ☐ Fibrosarcoma
- ☐ Synovial sarcoma
- ☐ Hemangiosarcoma
- ☐ Lymphangiosarcoma
- ☐ Neurogenic sarcoma
- ☐ Melanoma
- ☐ Central nervous system tumors (include CNS PNET)
- ☐ Medulloblastoma
- ☐ Neuroblastoma
- ☐ Retinoblastoma
- ☐ Mediastinal neoplasm, specify:_____
- ☐ Other solid tumor, specify:_____

Status at Transplantation:

- ☐ Untreated (upfront)
- ☐ Primary refractory
- ☐ Complete remission (CR)
- ☐ 1st very good partial response (VGPR1)
- ☐ 1st partial response (PR1)
- ☐ Relapse
- ☐ Adjuvant

Number
(complete only for CR or relapse)
- ☐ 1st
- ☐ 2nd
- ☐ 3rd or higher

Sensitivity to Chemotherapy
(complete only for relapse)
- ☐ Sensitive
- ☐ Resistant
- ☐ Untreated
- ☐ Unknown

CR=complete remission, PR=partial remission, VGPR=very good partial response, MR=minimal response

Transplant Essential Data
First Report: 100 Days Post Transplant
Disease Classification Sheet 5

PATIENT IDENTIFICATION
Hospital Unique Patient Number: _____

CENTER IDENTIFICATION
Center Identification Code:
IBMTR/ABMTR _____

INHERITED DISORDERS OF METABOLISM

Classification:

- ☐ Osteopetrosis (malignant infantile osteopetrosis)
- ☐ Lesch-Nyhan (HGPRT deficiency)
- ☐ Neuronal ceriod – lipofuscinosis (Batten disease)
- ☐ Mucopolysaccharidosis, NOS
- ☐ Hurler syndrome (IH)
- ☐ Scheie syndrome (IS)
- ☐ Hunter syndrome (II)
- ☐ Sanfilippo (III)
- ☐ Morquio (IV)
- ☐ Maroteaux-Lamy (VI)
- ☐ B-glucuronidase deficiency (VII)
- ☐ Mucopolysaccharidosis (V)
- ☐ Mucolipidoses, NOS
- ☐ Gaucher disease
- ☐ Metachromatic leukodystrophy (MLD)
- ☐ Adrenoleukodystrophy (ALD)
- ☐ Krabbe disease (globoid leukodystrophy)
- ☐ Neimann-Pick disease
- ☐ I-cell disease
- ☐ Wolman disease
- ☐ Glucose storage disease
- ☐ Polysaccharide hydrolase abnormalities, NOS
- ☐ Aspartyl glucosaminuria
- ☐ Fucosidosis
- ☐ Mannosidosis
- ☐ Inherited Disorders of Metabolism, NOS
- ☐ Other inherited disorder of metabolism, specify:_____

IMMUNE DEFICIENCIES

Classification:

- ☐ ADA deficiency severe combined immune deficiency (SCID)
- ☐ Absence of T and B cells SCID
- ☐ Absence of T, normal B cell SCID
- ☐ Omenn syndrome
- ☐ Reticular dysgenesis
- ☐ Bare lymphocyte syndrome
- ☐ SCID, NOS
- ☐ SCID other, specify: _____
- ☐ Ataxia telangiectasia
- ☐ HIV infection
- ☐ Wiskott Aldrich syndrome
- ☐ DiGeorge anomaly
- ☐ Chronic granulomatous disease
- ☐ Chediak-Higashi syndrome
- ☐ Common variable immunodeficiency
- ☐ X-linked lymphoproliferative syndrome
- ☐ Leukocyte adhesion deficiencies
- ☐ Kostmann syndrome-congenital neutropenia
- ☐ Neutrophil actin deficiency
- ☐ Cartilage hair hypoplasia
- ☐ CD 40 Ligand deficiency
- ☐ Immune Deficiencies, NOS
- ☐ Other immune deficiency, specify: _____

Transplant Essential Data
First Report: 100 Days Post Transplant
Disease Classification Sheet 6

PATIENT IDENTIFICATION
Hospital Unique Patient Number: _____

CENTER IDENTIFICATION
Center Identification Code:
IBMTR/ABMTR _____

AUTOIMMUNE DISORDERS

Classification	Involved Organs/Clinical Problem(s) *(Check all that apply)*	Primary Reason(s) for Transplant *(Check all that apply)*	Miscellaneous Labs *(Check all that apply)*
Connective Tissue Disease			
☐ Systemic sclerosis	☐ diffuse cutaneous ☐ limited cutaneous ☐ lung parenchyma ☐ pulmonary hypertension ☐ systemic hypertension ☐ renal (biopsy type:_____) ☐ esophagus ☐ other GI Tract ☐ Raynaud ☐ CREST ☐ other, specify:_____	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	Scl 70 positive ☐ ACA positive ☐
☐ Systemic lupus erythematosus	☐ renal (biopsy type:_____) ☐ CNS (type:_____) ☐ PNS (type:_____) ☐ lung ☐ serositis ☐ arthritis ☐ skin (type:_____) ☐ hematological (type:_____) ☐ vasculitis (type:_____) ☐ other, specify:_____	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	ds DNA ☐ (____) complement ☐ (____) other ☐ (____)
☐ Sjögren syndrome	☐ SICCA ☐ exocrine gland swelling ☐ other organ lymphocytic infiltration ☐ lymphoma, paraproteinemia ☐ other, specify:_____	☐ ☐ ☐ ☐ ☐	
☐ Polymyositis-dermatomyositis	☐ proximal weakness ☐ generalized weakness (including bulbar) ☐ pulmonary fibrosis ☐ vasculitis (type:_____) ☐ malignancy (type:_____) ☐ other, specify:_____	☐ ☐ ☐ ☐ ☐ ☐	CPK ☐ typical biopsy ☐ typical EMG ☐ typical rash (DM) ☐
☐ Antiphospholipid syndrome	☐ thrombosis (type:_____) ☐ CNS (type:_____) ☐ abortion ☐ skin (livido, vasculitis) ☐ hematological (type:_____) ☐ other, specify:_____	☐ ☐ ☐ ☐ ☐ ☐	anticardiolipin IgG ☐ anticardiolipin IgM ☐
☐ Other connective tissue disease, specify:_____			
Vasculitis			
☐ Wegener granulomatosis	☐ upper respiratory tract ☐ pulmonary ☐ renal (biopsy type:_____) ☐ skin ☐ other, specify:_____	☐ ☐ ☐ ☐ ☐	c-ANCA positive ☐
☐ Polyarteritis nodosa ☐ Classical ☐ Microscopic	☐ renal (type:_____) ☐ mononeuritis multiplex ☐ pulmonary hemorrhage ☐ skin ☐ GI Tract ☐ other, specify:_____	☐ ☐ ☐ ☐ ☐ ☐	p-ANCA positive ☐ c-ANCA positive ☐ hepatitis serology ☐

NOTE: *Transplant Essential Data should be submitted at time of mobilization for all patients with autoimmune disease*

Transplant Essential Data
First Report: 100 Days Post Transplant
Disease Classification Sheet 7

PATIENT IDENTIFICATION
Hospital Unique Patient Number: _____

CENTER IDENTIFICATION
Center Identification Code:
IBMTR/ABMTR _____

AUTOIMMUNE DISORDERS

Classification	Involved Organs/Clinical Problem(s) *(Check all that apply)*	Primary Reason(s) for Transplant *(Check all that apply)*	Miscellaneous Labs *(Check all that apply)*
Other vasculitis			
❑ Churg-Strauss			
❑ Giant cell arteritis			
❑ Takayasu			
❑ Behçet's Syndrome			
❑ overlap necrotizing arteritis			
❑ other vasculitis, specify:_____			
Arthritis			
❑ Rheumatoid arthritis	❑ destructive arthritis	❑	
	❑ necrotizing vasculitis	❑	
	❑ eye (type:_____)	❑	
	❑ pulmonary	❑	
	❑ extra-articular (specify:_____)	❑	
	❑ other, specify:_____	❑	
❑ Psoriatic arthritis/psoriasis	❑ destructive arthritis	❑	
	❑ psoriasis	❑	
	❑ other, specify:_____	❑	
❑ Juvenile idiopathic arthritis: systemic (Stills disease)			
❑ Juvenile idiopathic arthritis: Oligoarticular			
❑ Juvenile idiopathic arthritis: Polyarticular			
❑ Juvenile idiopathic arthritis: Other, specify:_____			
❑ Other, arthritis, specify:_____			
Multiple sclerosis			
❑ Multiple sclerosis (MS)	❑ primary progressive	❑	
	❑ secondary progressive	❑	
	❑ relapsing/remitting	❑	
	❑ other specify:_____		
Other Neurological Autoimmune Disease			
❑ Myasthenia gravis			
❑ Other autoimmune neurological disorder, specify:_____			
Hematological Autoimmune Disease			
❑ Idiopathic thrombocytopenic purpura (ITP)			
❑ Hemolytic anemia			
❑ Evan syndrome			
❑ other autoimmune cytopenia, specify:_____			
Bowel Disease			
❑ Crohn's disease			
❑ Ulcerative colitis			
❑ Other autoimmune bowel disorder, specify:_____			

TED-01 (6/06) Page 8 of 8

CIC: Unique Patient Number (UPN): .....

Minimum Essential Data - A

First report - 100 days after transplant

PRIMARY DISEASE DIAGNOSIS: .....

TYPE OF TRANSPLANT: ☐ Auto ☐ Allo ☐ Syngeneic

DATE OF TRANSPLANT: ..... - ..... - .....
yyyy mm dd

CENTRE IDENTIFICATION

EBMT Code (CIC): ....

CIBMTR/ABMTR Code .....

Hospital: ..... Unit: .....

Contact person.....

Phone:.....

Fax:.....

e-mail: .....

REPORT INFORMATION

Date of this Report: ..... - ..... - .....
yyyy mm dd

Patient asked to consent to data submission? ☐ Yes ☐ No

Is this a non-transplant registration? ☐ Yes ☐ No

Is registration to be sent to CIBMTR ☐ Yes ☐ No

IUBMID *(only if data is to be sent to CIBMTR)*:_____

Patient following national / international study / trial:
☐ Yes ☐ No ☐ Unknown

Name of study / trial .... Num Pat.....

PATIENT IDENTIFICATION

Unique Patient Number or Code: .....

Compulsory, registrations will not be accepted without this item

Initials: ....._..... (first name(s) _surname(s))

Date of Birth: ..... - ..... - .....
yyyy mm dd

Sex: ☐ Male ☐ Female

DISEASE

Date of initial diagnosis: ..... - ..... - .....
yyyy mm dd

Disease classification sheet: **Complete and attach only the relevant page with date and status at transplantation**

Performance score: ☐ Good (Karn≥80; ECOG 0-1; Lansky≥80) ☐ Poor (Karn<80; ECOG 2-3; Lansky<80) ☐ Unknown

Type of Transplant:
- ☐ AUTOlogous *(self)*
- ☐ ALLOgeneic
  - ☐ Syngeneic *(monozygotic twin)*
  - ☐ HLA-identical sibling *(may include non monozygotic twin)*
  - ☐ HLA-matched other relative
  - ☐ HLA-mismatched relative
  - ☐ HLA-matched unrelated donor
  - ☐ HLA-mismatched unrelated donor

Donor Sex *(for allografts)*: ☐ Male ☐ Female

Multiple donors *(check all relevant HLA types above)*
☐ Yes ☐ No

Source of Stem Cells *(check all that apply)*:
☐ Bone Marrow ☐ Peripheral Blood
☐ Cord Blood ☐ Other: .....

Chronological no. of transplant for this patient .....

Date of previous transplant: ..... - ..... - .....
yyyy mm dd

Type of previous transplant:_____ ☐ N/A

Was the current transplant part of a planned multiple graft protocol? ☐ Yes ☐ No ☐ Unknown

Graft manipulation ex-vivo (including T-cell depletion) *(other than for RBC removal or volume reduction)*
☐ Yes ☐ No ☐ Unknown

TRANSPLANTATION (cont.)

Conditioning regimen:

Non myeloablative/Reduced intensity ☐ Yes ☐ No

Total Body Irradiation ☐ Yes ☐ No

AFTER TRANSPLANTATION

Engraftment *(Neutrophils ≥0.5X10⁹ /L)*:

☐ Yes: Date of engraftment : ..... - ..... - .....
yyyy mm dd

☐ No: Date of last assessment : ..... - ..... - .....

☐ Never below *yyyy mm dd*

Acute Graft Versus Host Disease:

Maximum Grade: ☐ Absent ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ Unknown ☐ Not applicable

Additional cell therapy given *(not for relapse or progression)*
(if additional transplant given, submit separate registration)

☐ Yes ☐ No ☐ Unknown

Date of first infusion: ....
(may be the same as transplant date) yyyy mm dd

Type of cell(s): *(check all that apply)*
☐ Lymphocytes ☐ Fibroblasts
☐ Dendritic cells ☐ Other .....

Best disease status (response) after transplant

☐ Continued complete remission (CR)

☐ CR achieved: Date achieved : ..... - ..... - .....
yyyy mm dd

☐ Never in CR: Date assessed: ..... - ..... - .....☐ Unknown
yyyy mm dd

DATE OF LAST CONTACT

Date of last follow up or death: ..... - ..... - .....
yyyy mm dd

PATIENT AND DISEASE STATUS AT FOLLOW UP

First Relapse or Progression after transplant:
☐ Yes ☐ No ☐ Continuous progression ☐ Unknown

Tick all methods used for the assessment with the dates on which they were used, adding whether relapse/progression was first detected for that method on the date indicated *(complete only for relapse)*

Molecular: Date ..... - ..... - .....
☐ Done ☐ Not done *yyyy mm dd*
Relapse/progression first detected with this method: ☐ Yes ☐ No

Cytogenetic: Date ..... - ..... - .....
☐ Done ☐ Not done *yyyy mm dd*
Relapse/progression first detected with this method: ☐ Yes ☐ No

Haematological/clinical: Date ..... - ..... - .....
☐ Done ☐ Not done *yyyy mm dd*
Relapse/progression first detected with this method: ☐ Yes ☐ No

Survival Status:
☐ Alive ☐ Dead ☐ Died before transplant
Check here if patient lost to follow up ☐

Main Cause of Death *(check only one main cause)*:
☐ Relapse or Progression
☐ Transplantation Related Cause
(check as many as appropriate):
- ☐ Acute GVHD
- ☐ Cardiac Toxicity
- ☐ Rejection/Poor graft function
- ☐ Infection
- ☐ Pulmonary toxicity
- ☐ Veno occlusive disorder
- ☐ Post transplant lymphoproliferative disorder
- ☐ Other:.....

☐ Unknown
☐ Other: .....

CIC: Unique Patient Number (UPN): .....

Minimum Essential Data - A

Follow up report: 1 year post transplant and annually thereafter

PRIMARY DISEASE DIAGNOSIS: .....

TYPE OF TRANSPLANT: ☐ Auto ☐ Allo ☐ Syngeneic

CENTRE IDENTIFICATION

EBMT Code (CIC): ....
CIBMTR/ABMTR Code .....
Hospital: .....
Unit: .....
Contact person.....
Phone:.....
Fax:.....
e-mail: .....

REPORT INFORMATION

Date of this Report: ..... - ..... - .....
yyyy mm dd
Patient asked to consent to data submission? ☐
(if not consented before, i.e. pre-2003 registrations)

Check here if follow up is to be passed on to the CIBMTR☐

Patient following national / international study / trial:
☐ Yes ☐ No ☐ Unknown
Name of study / trial .... Num Pat ...

PATIENT AND TRANSPLANT IDENTIFICATION

Unique Patient Number or Code: .....
(Compulsory, registrations will not be accepted without this item)
Initials: ....._..... (first name(s) _surname(s))

Date of Birth: ..... - ..... - .....
yyyy mm dd
Sex: ☐ Male ☐ Female
Date of the transplant to which this follow up refers to:
..... - ..... - .....
yyyy mm dd

AFTER TRANSPLANTATION

(if information not submitted with first report)

Engraftment *(Neutrophils >0.5X10⁹ /L)*:
☐ Previously reported
☐ Yes: Date of engraftment : ..... - ..... - .....
yyyy mm dd
☐ No: Date of last assessment : ..... - ..... - .....
yyyy mm dd
☐ Unknown

Acute Graft Versus Host Disease:
Maximum Grade:
☐ Previously reported
☐ Absent ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ Unknown

Best disease status after transplant:
☐ Previously reported
☐ Continued complete remission (CR)
☐ CR achieved: Date CR: ..... - ..... - .....
☐ Never in CR *yyyy mm dd*
☐ Unknown
Date response assessed: ..... - ..... - .....
yyyy *mm dd*

DATE OF LAST CONTACT

Date of last follow up or death: ..... - ..... - .....
yyyy mm dd

LATE COMPLICATIONS OF TRANSPLANT

Late graft failure
Did late graft failure occur? ☐ Yes ☐ No
Chronic Graft Versus Host Disease *(allografts only)*
☐ Yes ☐ No ☐ Unknown
If yes: Date first evidence of cGvHD: ..... - ..... -.....
yyyy mm dd
Maximum extent up to date of this follow up
☐ Limited ☐ Extensive ☐ Unknown

LATE COMPLICATIONS (cont.)

Secondary disease or lymphoproliferative disease?
☐ Yes: Diagnosis: .....
Date of diagnosis: ..... - ..... - .....
yyyy mm dd
☐ No: Date assessed : ..... - ..... - .....
yyyy mm dd
☐ Unknown

ADDITIONAL TREATMENT

Additional cell therapy given since last report:
(can be for relapse or progression; if additional transplant given, submit separate registration)
☐ Yes ☐ No ☐ Unknown
Date of first infusion: ....
yyyy mm dd
Type of cell: *(check all that apply)*
☐ Lymphocytes ☐ Fibroblasts
☐ Dendritic cells ☐ Other .....

DISEASE STATUS

First Relapse or Progression after transplant:
☐ Yes ☐ No ☐ Continuous progression ☐ Unknown
☐ Previously reported
Tick all methods used for the assessment with the dates on which they were used, adding whether relapse/progression was first detected for that method on the date indicated *(complete only for relapse)*

Molecular: Date ..... - ..... - .....
☐ Done ☐ Not done *yyyy mm dd*
Relapse/progression first detected with this method: ☐ Yes ☐ No

Cytogenetic: Date ..... - ..... - .....
☐ Done ☐ Not done *yyyy mm dd*
Relapse/progression first detected with this method: ☐ Yes ☐ No

Haematological/clinical: Date ..... - ..... - .....
☐ Done ☐ Not done *yyyy mm dd*
Relapse/progression first detected with this method: ☐ Yes ☐ No

CONCEPTION

Has patient or partner become pregnant after this transplant?
☐ Yes ☐ No ☐ Unknown

PATIENT STATUS

Survival Status:
☐ Alive ☐ Dead

Check here if patient lost to follow up ☐

Current disease status
☐ Complete remission (CR)
☐ Not in remission

Last date disease assessed: ..... - ..... - .....
yyyy mm dd
Main Cause of Death *(check only one main cause)*:
☐ Relapse or Progression
☐ Secondary malignancy
☐ Transplantation Related Cause
(check as many as appropriate):
☐ Chronic GVHD ☐ Cardiac Toxicity
☐ Rejection/Poor graft function ☐ Infection
☐ Pulmonary toxicity ☐ Veno occlusive disorder
☐ Post transplant lymphoproliferative disorder
☐ Other:.....
☐ Unknown
☐ Other: .....

CIC: Unique Patient Number (UPN): .....

Minimum Essential Data - A

First report - 100 days after transplant

DISEASE CLASSIFICATION SHEET 1

EBMT Centre Identification Code (CIC) ..... Hospital Unique Patient Number .....
CIBMTR/ABMTR Code .....

ACUTE LEUKEMIAS

Classification:

Acute Myelogenous Leukemia (AML)	Acute Lymphoblastic Leukemia (ALL)	Other Acute Leukemias
☐ M0	☐ ALL B-lineage	☐ Acute undifferentiated
☐ M1	☐ ALL T-lineage	☐ Acute biphenotypic
☐ M2	☐ Mature B cell (L3)	☐ Acute mast cell leukemia
☐ M3	☐ ALL unspecified	☐ Other, specify: _____
☐ M4	☐ T-cell granular lymphocytic leukaemia	
☐ M5	☐ Aggressive NK-cell leukaemia	
☐ M6	☐ Adult T-cell lymphoma/leukaemia (HTLV1+)	
☐ M7	☐ Other ALL, specify:_____	
☐ Other AML, specify:_____		
☐ AML unspecified		

☐ Transformed from MDS → *Complete MDS section on DiseaseClassification Sheet 2. Do not complete the remainder of AML*

Secondary origin?: ☐ Yes: Disease related to prior exposure to therapeutic drugs or radiation
☐ No
☐ Unknown

Date of this transplant: ..... - ..... - .....
yyyy mm dd

Status at Transplantation:

STATUS	NUMBER	FOR COMPLETE REMISSION ONLY				
	(complete only for CR or relapse)		Yes	No	Not evaluated	Unknown
☐ Untreated						
☐ Primary induction failure	☐ 1st	Cytogenetic	☐	☐	☐	☐
☐ Complete remission (CR)	☐ 2nd	Molecular	☐	☐	☐	☐
☐ Relapse	☐ 3rd or higher					

CHRONIC MYELOGENOUS LEUKEMIA (CML)

Classification:

☐ CML, Translocation (9;22) negative
☐ CML, Translocation (9;22) positive
☐ CML, not otherwise specified

Date of this transplant: ..... - ..... - .....
yyyy mm dd

Status at Transplantation:

PHASE	NUMBER	FOR CHRONIC PHASE ONLY, TYPE OF REMISSION *(check all that apply)*				
☐ Chronic phase (CP)	☐ 1st	Haematological:	☐ Yes	☐ No, stable phase		
☐ Accelerated phase	☐ 2nd	Cytogenetic:	☐ Complete	☐ No	☐ Not eval.	☐ Unknown
☐ Blast crisis	☐ 3rd or higher	Molecular (bcr/abl):	☐ Yes	☐ No	☐ Not eval.	☐ Unknown
		Other:.....				

OTHER LEUKEMIAS

Classification:

☐ Chronic lymphocytic leukemia (CLL), B-cell/ small lymphocytic lymphoma
☐ CLL, T-cell
☐ CLL, not otherwise specified
☐ Prolymphocytic Leukemia
  ☐ B-cell
  ☐ T-cell
☐ Hairy Cell Leukemia
☐ Other leukemia, specify:_____

Date of this transplant: ..... - ..... - .....
yyyy mm dd

Status at Transplantation:

☐ Untreated
☐ Complete remission (CR)
☐ Partial remission (PR)
☐ No response/stable
☐ Progression

CIC: Unique Patient Number (UPN): .....

Minimum Essential Data - A

First report - 100 days after transplant

DISEASE CLASSIFICATION SHEET 2

EBMT Centre Identification Code (CIC) ..... Hospital Unique Patient Number .....
CIBMTR/ABMTR Code .....

MYELODYSPLASTIC and MYELOPROLIFERATIVE SYNDROMES

Classification:

Myelodysplastic Syndromes (MDS)

At diagnosis	At transplantation
☐	☐ RA
☐	☐ RARS
☐	☐ RAEB
☐	☐ RAEB-t
	☐ Transformed to AML
☐	☐ MDS not otherwise specified
☐	☐ Other, specify:_____

Myeloproliferative Syndromes (MPS)

At diagnosis	At transplantation
☐	☐ Polycythemia vera
☐	☐ Essential or primary thrombocythemia
☐	☐ Myelofibrosis with myeloid metaplasia
☐	☐ Acute myelofibrosis or myelosclerosis
☐	☐ MPS not otherwise specified
☐	☐ Other, specify:_____

Myelodysplastic and Myeloproliferative Syndrome (MDS/MPS)

At diagnosis	At transplantation
☐	☐ Chronic myelomonocytic leukaemia (CMMoL, CMML)
☐	☐ Juvenile myelomonocytic leukaemia (JMML, JCML, JCMML)
☐	☐ Other, specify _____

Date of this transplant: ..... - ..... - .....

Status at Transplantation:

- ☐ Untreated (Supportive care only)
- ☐ Treatment without intent to achieve complete remission (CR)
- ☐ Treatment with intent to achieve a CR – CR not achieved
- ☐ Treatment with intent to achieve a CR – CR achieved and sustained
- ☐ Relapse after CR

NUMBER *(complete for CR or relapse)*

- ☐ 1st
- ☐ 2nd
- ☐ 3rd or higher

ANAEMIA

Classification:

- ☐ Acquired Severe Aplastic Anaemia (SAA), not otherwise specified
  - ☐ Acquired SAA, secondary to hepatitis
  - ☐ Acquired SAA, secondary to toxin/other drug
  - ☐ Amegakaryocytosis acquired (not congenital)
  - ☐ Acquired Pure Red Cell Aplasia (PRCA) (not congenital)
  - ☐ Other acquired cytopenic syndrome, specify: _____
- ☐ Fanconi anaemia
- ☐ Diamond-Blackfan anaemia (congenital PRCA)
- ☐ Schwachman-Diamond
- ☐ Other constitutional anaemia, specify: _____
- ☐ Paroxysmal nocturnal hemoglobinuria (PNH)

Date of this transplant: ..... - ..... - .....

HEMOGLOBINOPATHY

Classification:

- ☐ Thalassemia
- ☐ Sickle cell disease
- ☐ Other hemoglobinopathy, specify: _____

Date of this transplant: ..... - ..... - .....

PLATELET DISORDERS

Classification:

- ☐ Congenital amegakaryocytosis / congenital thrombocytopenia
- ☐ Glanzmann thrombasthenia
- ☐ Other inherited platelet abnormalities, specify: _____

Date of this transplant: ..... - ..... - .....

HISTIOCYTIC DISORDERS

Classification:

- ☐ Histiocytic disorders, not otherwise specified
- ☐ Langerhans Cell Histiocytosis (Histiocytosis-X)
- ☐ Malignant histiocytosis
- ☐ Familial erythro/hemophagocytic lymphohistiocytosis (FELH)
- ☐ Hemophagocytosis (reactive or viral associated)
- ☐ Other, specify:_____

Date of this transplant: ..... - ..... - .....

CIC: Unique Patient Number (UPN): .....

Minimum Essential Data - A

First report - 100 days after transplant

DISEASE CLASSIFICATION SHEET 3

EBMT Centre Identification Code (CIC) ..... Hospital Unique Patient Number .....
CIBMTR/ABMTR Code .....

LYMPHOMAS

Classification:

☐ **Non-Hodgkin's lymphoma (NHL)**

B-cell Neoplasms

- ☐ Follicular lymphoma
  - ☐ Grade I ☐ Grade II ☐ Grade III ☐ Unknown
- ☐ Mantle cell lymphoma
- ☐ Extranodal marginal zone of MALT type
- ☐ Diffuse large B-cell lymphoma
- ☐ Mediastinal large cell lymphoma
- ☐ Burkitt's lymphoma/Burkitt cell leukemia
- ☐ Precursor B-lymphoblastic leukemia/lymphoma
- ☐ Lymphoplasmacytic lymphoma *(including Waldenstrom)*
- ☐ Splenic marginal zone B-cell lymphoma
- ☐ Nodal marginal zone B-cell lymphoma
- ☐ Other, specify:_____

T-cell & NK-cell Neoplasms

- ☐ Angioimmunoblastic (AILD)
- ☐ Peripheral (all variants)
- ☐ Anaplastic large-cell, T/null cell, primary cutaneous
- ☐ Anaplastic large-cell, T/null cell, primary systemic
- ☐ Precursor T-lymphoblastic lymphoma/leukemia
- ☐ Extranodal NK/T-cell lymphoma, nasal type
- ☐ Enteropathy-type T-cell lymphoma
- ☐ Hepatosplenic gamma-delta T-cell lymphoma
- ☐ Subcutaneous panniculitis-like T-cell lymphoma
- ☐ Mycosis fungoides
- ☐ Sezary syndrome
- ☐ Other, specify:_____

☐ **Hodgkin**
☐ **Other** _____

Date of this transplant: ..... - ..... - .....
yyyy mm dd

Status at Transplantation:

STATUS
- ☐ Untreated
- ☐ Primary refractory
- ☐ Complete remission (CR)
  - ☐ Confirmed ☐ Unconfirmed (CRU*)
- ☐ 1st Partial response (PR1)
- ☐ 1st Very good partial response (VGPR1)
- ☐ Relapse
- ☐ Progression

NUMBER *(complete only for CR or relapse)*
- ☐ 1st
- ☐ 2nd
- ☐ 3rd or higher

SENSITIVITY TO CHEMOTHERAPY *(complete only for relapse)*
- ☐ Sensitive
- ☐ Resistant
- ☐ Untreated
- ☐ unknown

*CRU – complete response with persistent scan abnormalities of unknown significance

PLASMA CELL DISORDERS including MULTIPLE MYELOMA

Classification
- ☐ Multiple myeloma - IgG
- ☐ Multiple myeloma - IgA
- ☐ Multiple myeloma – IgD
- ☐ Multiple myeloma – IgE
- ☐ Multiple myeloma-light chain
- ☐ Multiple myeloma-non-secretory

LIGHT CHAIN TYPE
- ☐ Kappa
- ☐ Lambda

SALMON & DURIE
STAGE AT DIAGNOSIS *(Multiple Myeloma only)*
- ☐ I and ☐ A
- ☐ II ☐ B
- ☐ III

- ☐ Plasma cell leukemia
- ☐ Solitary plasmacytoma
- ☐ Primary amyloidosis
- ☐ Other, specify:_____

Date of this transplant: ..... - ..... - .....
yyyy mm dd

Status at Transplantation:
- ☐ Untreated
- ☐ Complete remission (CR)
- ☐ Partial remission (PR)
- ☐ Minimal response (MR)
- ☐ Relapse / Progression
- ☐ No change / stable disease

NUMBER *(complete for CR, PR or relapse)*
- ☐ 1st
- ☐ 2nd
- ☐ 3rd or higher

CIC: Unique Patient Number (UPN): .....

Minimum Essential Data - A

First report - 100 days after transplant

DISEASE CLASSIFICATION SHEET 4

EBMT Centre Identification Code (CIC) ..... Hospital Unique Patient Number .....
CIBMTR/ABMTR Code .....

BREAST CANCER

Staging at Diagnosis

METASTASES
- ☐ No distant metastases
- ☐ Metastatic

STAGE
- ☐ 0
- ☐ I
- ☐ II
- ☐ III

CLASSIFICATION:
- ☐ Inflammatory
- ☐ Non-inflammatory

Date of this transplant: ..... - ..... - .....

Status at Transplantation:
- ☐ Adjuvant (Stage II, III only)
- ☐ Untreated (upfront)
- ☐ Primary refractory
- ☐ Complete remission (CR)
  - ☐ Confirmed ☐ Unconfirmed (CRU*)
- ☐ 1st Very good partial response (VGPR1)
- ☐ 1st Partial response (PR1)
- ☐ Relapse
  - ☐ Local ☐ Metastatic

NUMBER *(complete only for CR or relapse)*
- ☐ 1st
- ☐ 2nd
- ☐ 3rd or higher

SENSITIVITY TO CHEMOTHERAPY *(complete only for relapse)*
- ☐ Sensitive
- ☐ Resistant
- ☐ Untreated
- ☐ Unknown

*CRU – complete response with persistent scan abnormalities of unknown significance

OTHER MALIGNANCIES

Classification:
- ☐ Bone sarcoma (excluding Ewing sarcoma)(include sarcoma PNET)
- ☐ Central nervous system tumors (include CNS PNET)
- ☐ Cervical
- ☐ Colorectal
- ☐ Ewing sarcoma
- ☐ External genitalia
- ☐ Fibrosarcoma
- ☐ Gastric
- ☐ Germ cell tumour, extragonadal only
- ☐ Head and neck
- ☐ Hemangiosarcoma
- ☐ Hepatobiliary
- ☐ Kidney and urinary tract
- ☐ Leiomyosarcoma
- ☐ Liposarcoma
- ☐ Lung cancer, non-small cell
- ☐ Lung cancer, small cell
- ☐ Lung cancer, not otherwise specified
- ☐ Lymphangiosarcoma
- ☐ Mediastinal neoplasm
- ☐ Medulloblastoma
- ☐ Melanoma
- ☐ Neuroblastoma
- ☐ Neurogenic sarcoma
- ☐ Other
- ☐ Ovarian
- ☐ Pancreas
- ☐ Prostate
- ☐ Retinoblastoma
- ☐ Rhabdomyosarcoma
- ☐ Sarcoma not otherwise specified
- ☐ Soft tissue sarcoma (include sarcoma PNET)
- ☐ Synovial sarcoma
- ☐ Testicular
- ☐ Thymoma
- ☐ Uterus
- ☐ Vagina
- ☐ Wilm tumour
- ☐ Other, specify .....

Date of this transplant: ..... - ..... - .....
Yyyy mm dd

Status at Transplantation:
- ☐ Adjuvant
- ☐ Untreated (upfront)
- ☐ Primary refractory
- ☐ Complete remission (CR)
- ☐ 1st Very good partial response (VGPR1)
- ☐ 1st Partial response (PR1)
- ☐ Relapse

NUMBER *(complete only for CR or relapse)*
- ☐ 1st
- ☐ 2nd
- ☐ 3rd or higher

SENSITIVITY TO CHEMOTHERAPY *(complete only for relapse)*
- ☐ Sensitive
- ☐ Resistant
- ☐ Untreated

EBMT MED-A 2003 – *reformatted for Promise 2, modified 11 Oct 2006 - p. 6*

CIC: Unique Patient Number (UPN): .....

Minimum Essential Data - A

First report - 100 days after transplant

DISEASE CLASSIFICATION SHEET 5

EBMT Centre Identification Code (CIC) ..... Hospital Unique Patient Number .....
CIBMTR/ABMTR Code .....

INHERITED DISORDERS OF METABOLISM

Classification:

- ☐ Adrenoleukodystrophy
- ☐ Aspartyl glucosaminuria
- ☐ B-glucuronidase deficiency (VII)
- ☐ Fucosidosis
- ☐ Gaucher disease
- ☐ Glucose storage disease
- ☐ Hunter syndrome (II)
- ☐ Hurler syndrome (IH)
- ☐ I-cell disease
- ☐ Krabbe disease (globoid leukodystrophy)
- ☐ Lesch-Nyhan (HGPRT deficiency)
- ☐ Mannosidosis
- ☐ Maroteaux-Lamy (VI)
- ☐ Metachromatic leukodystrophy
- ☐ Morquio (IV)
- ☐ Mucolipidoses, not otherwise specified
- ☐ Mucopolysaccharidosis (V)
- ☐ Mucopolysaccharidosis, not otherwise specified
- ☐ Niemann-Pick disease
- ☐ Neuronal ceriod – lipofuscinosis (Batten disease)
- ☐ Osteopetrosis (malignant infantile osteopetrosis)
- ☐ Polysaccharide hydrolase abnormalities, unspecified
- ☐ Sanfilippo (III)
- ☐ Scheie syndrome (IS)
- ☐ Wolman disease
- ☐ Other, specify: .....
- ☐ Unspecified

Date of this transplant: ..... - ..... - .....
yyyy mm dd

IMMUNE DEFICIENCIES

Classification:

- ☐ Absence of T and B cells SCID
- ☐ Absence of T, normal B cell SCID
- ☐ ADA deficiency severe combined immune deficiency (SCID)
- ☐ Ataxia telangiectasia
- ☐ Bare lymphocyte syndrome
- ☐ Cartilage hair hypoplasia
- ☐ CD 40 Ligand deficiency
- ☐ Chediak-Higashi syndrome
- ☐ Chronic granulomatous disease
- ☐ Common variable immunodeficiency
- ☐ DiGeorge anomaly
- ☐ HIV infection
- ☐ Kostmann syndrome-congenital neutropenia
- ☐ Leukocyte adhesion deficiencies
- ☐ Neutrophil actin deficiency
- ☐ Omenn syndrome
- ☐ Reticular dysgenesis
- ☐ SCID other, specify: .....
- ☐ SCID, not otherwise specified
- ☐ Wiskott Aldrich syndrome
- ☐ X-linked lymphoproliferative syndrome
- ☐ Other, specify: .....
- ☐ Immune Deficiencies, not otherwise specified

Date of this transplant: ..... - ..... - .....
yyyy mm dd

CIC: Unique Patient Number (UPN): .....

Minimum Essential Data - A

First report - 100 days after transplant

DISEASE CLASSIFICATION SHEET 6

NOTE: The MED-A First Report should be submitted at time of mobilisation for all patients with autoimmune diseases

EBMT Centre Identification Code (CIC) ..... Hospital Unique Patient Number .....
CIBMTR/ABMTR Code .....

Neurologist Name_____
Address_____
Fax_____ Email_____

AUTOIMMUNE DISORDERS – I

Classification	Involved Organs/Clinical Problem	Reason for Transplant	Miscellaneous
CONNECTIVE TISSUE DISEASE			
☐ Systemic sclerosis	☐ diffuse cutaneous	☐	☐ Scl 70 positive
	☐ limited cutaneous	☐	☐ ACA positive
	☐ lung parenchyma	☐	
	☐ pulmonary hypertension	☐	
	☐ systemic hypertension	☐	
	☐ renal (biopsy type:_____)	☐	
	☐ oesophagus	☐	
	☐ other GI tract		
	☐ Raynaud	☐	
	☐ CREST	☐	
	☐ other, specify:_____	☐	
☐ Systemic lupus erythematosus	☐ renal (biopsy type:_____)	☐	☐ ds DNA (_____)
	☐ CNS (type:_____)	☐	☐ complement (_____)
	☐ PNS (type:_____)	☐	☐ other (_____)
	☐ lung	☐	
	☐ serositis	☐	
	☐ arthritis	☐	
	☐ skin (type:_____)	☐	
	☐ haematological (type:_____)	☐	
	☐ vasculitis (type:_____)	☐	
	☐ other, specify:_____	☐	
☐ Sjögren syndrome	☐ SICCA	☐	
	☐ exocrine gland swelling	☐	
	☐ other organ lymphocytic infiltration	☐	
	☐ lymphoma, paraproteinemia	☐	
	☐ other, specify:_____	☐	
☐ Polymyositis-dermatomyositis	☐ proximal weakness	☐	☐ CPK
	☐ generalized weakness (including bulbar)	☐	☐ typical biopsy
	☐ pulmonary fibrosis	☐	☐ typical EMG
	☐ vasculitis (type:_____)	☐	☐ typical rash (DM)
	☐ malignancy (type:_____)	☐	
	☐ other, specify:_____	☐	
☐ Antiphospholipid syndrome	☐ thrombosis (type:_____)	☐	☐ anticardiolipin IgG
	☐ CNS (type:_____)	☐	☐ anticardiolipin IgM
	☐ abortion	☐	
	☐ skin (livido, vasculitis)	☐	
	☐ hematological (type:_____)	☐	
	☐ other, specify:_____	☐	
☐ other, specify:_____			

Date of this transplant: ..... - ..... - ..... (*yyyy - mm - dd*)

CIC: Unique Patient Number (UPN): .....

Minimum Essential Data - A

First report - 100 days after transplant

DISEASE CLASSIFICATION SHEET 7

NOTE: The MED-A First Report should be submitted at time of mobilisation for all patients with autoimmune diseases

EBMT Centre Identification Code (CIC) ..... Hospital Unique Patient Number .....
CIBMTR/ABMTR Code .....

AUTOIMMUNE DISORDERS – II

Classification	Involved Organs/Clinical Problem	Reason for Transplant	Miscellaneous

Neurologist Name_____
Address_____
Fax_____ Email_____

VASCULITIS

☐ Wegener granulomatosis	☐ upper respiratory tract	☐	☐ c-ANCA positive
	☐ pulmonary	☐	
	☐ renal (biopsy type:_____)	☐	
	☐ skin	☐	
	☐ other, specify:_____	☐	
☐ Classical polyarteritis nodosa			
	☐ renal (type:_____)	☐	
☐ Classical	☐ mononeuritis multiplex	☐	☐ p-ANCA positive
☐ Microscopic	☐ pulmonary haemorrhage	☐	☐ c-ANCA positive
	☐ skin	☐	☐ hepatitis serology
	☐ GI tract	☐	
	☐ other, specify:_____	☐	

Other vasculitis:
☐ Churg-Strauss
☐ Giant cell arteritis
☐ Takayasu
☐ Behçet's syndrome
☐ overlap necrotising arteritis
☐ other, specify:_____

ARTHRITIS

☐ Rheumatoid arthritis	☐ destructive arthritis	☐
	☐ necrotising vasculitis	☐
	☐ eye (type:_____)	☐
	☐ pulmonary	☐
	☐ extra articular (specify:_____)	☐
	☐ other, specify:_____	☐
☐ Psoriatic arthritis/psoriasis	☐ destructive arthritis	☐
	☐ psoriasis	☐
	☐ other, specify:_____	☐

☐ Juvenile idiopathic arthritis (JIA): systemic (Stills disease)
☐ Juvenile idiopathic arthritis: Oligoarticular
☐ Juvenile idiopathic arthritis: Polyarticular
☐ Juvenile idiopathic arthritis: other, specify:_____
☐ Other arthritis: .....

MULTIPLE SCLEROSIS

☐ Multiple sclerosis	☐ primary progressive	☐
	☐ secondary progresive	☐
	☐ relapsing/remitting	☐
	☐ other:_____	☐

OTHER NEUROLOGICAL AUTOIMMUNE DISEASE
☐ Myasthenia gravis
☐ Other autoimmune neurological disorder, specify:_____

HAEMATOLOGICAL AUTOIMMUNE DISEASES
☐ Idiopathic thrombocytopenic purpura (ITP)
☐ Hemolytic anemia
☐ Evan syndrome
☐ other autoimmune cytopenia, specify:_____

BOWEL DISEASE
☐ Crohn's disease
☐ Ulcerative colitis
☐ Other autoimmune bowel disease, specify:_____

Date of this transplant: ..... - ..... - ..... (*yyyy - mm - dd*)

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FACT ACCREDITATION OFFICE
University of Nebraska Medical Center
986065 Nebraska Medical Center
Omaha, NE 68198-6065

Phone: (402) 559-1950
Fax: (402) 559-1951
E-mail: fact@unmc.edu
Website: www.factwebsite.org