

INTERNATIONAL STANDARDS FOR CORD BLOOD COLLECTION, BANKING, AND RELEASE FOR ADMINISTRATION ACCREDITATION MANUAL



**Sixth Edition
July 2016**

NOTICE

These Standards are designed to provide minimum guidelines for Cord Blood Banks, facilities, and individuals performing cord blood donor management, collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, and distribution, or providing support services for such procedures. These Standards are not intended to establish best practices or include all procedures and practices that a Cord Blood Bank, facility, or individual should implement if the standard of practice in the community or Applicable Law establish additional requirements. Each Cord Blood Bank, facility, and individual should analyze its practices and procedures to determine whether additional standards apply. Compliance with the Standards is not an exclusive means of complying with the standard of care in the industry or community or with local, national, or international laws or regulations.

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

This page intentionally left blank.

TABLE OF CONTENTS

		Page Number
	INTRODUCTION	1
PART A	TERMINOLOGY, TENETS, ABBREVIATIONS, AND DEFINITIONS	5
	A1 Terminology	6
	A2 Tenets	6
	A3 Abbreviations	6
	A4 Definitions	7
PART B	CORD BLOOD BANK OPERATIONAL STANDARDS	19
	B1 General Requirements	20
	B2 Quality Management	23
	B3 Policies and Standard Operating Procedures	42
	B4 Facilities and Safety	55
	B5 Cord Blood Bank Operations	56
	B6 Coding and Labeling of Cord Blood Units	63
	B7 Equipment	74
	B8 Supplies and Reagents	78
	B9 Inventory Management	80
	B10 Inventory Transfer	81
	B11 Documents and Records Requirements	84
	B12 Interruption of Operations at Established Sites	92
PART C	CORD BLOOD DONOR MANAGEMENT AND COLLECTION STANDARDS	95
	C1 General Requirements	96

C2	Cord Blood Collection Personnel Requirements	103
C3	Policies and Standard Operating Procedures	105
C4	Informed Consent	108
C5	Maternal and Infant Donor Evaluation	114
C6	Cord Blood Collection	121
C7	Transportation and Shipping of Unmanipulated Cord Blood Units Between the Cord Blood Collection Site and the Cord Blood Processing Facility	126
PART D	CORD BLOOD PROCESSING STANDARDS	131
D1	Facility Requirements	132
D2	Policies and Standard Operating Procedures	138
D3	Cord Blood Processing	141
D4	Samples	147
D5	Cryopreservation	151
D6	Conditions for Storage	154
D7	Monitoring and Alarm Systems	160
D8	Disposition	162
D9	Cord Blood Unit Testing	167
D10	Maternal Testing	173
PART E	CORD BLOOD LISTING, SEARCH, SELECTION, RESERVATION, RELEASE, AND DISTRIBUTION STANDARDS	179
E1	General Requirements	180
E2	Review of Cord Blood Unit Records	182
E3	Cord Blood Unit Selection and Release for Administration	183
E4	Cord Blood Unit Distribution to a Clinical Program	187

E5	Transportation and Shipping of Cryopreserved Cord Blood Units	190
E6	Transportation and Shipping Records Requirements	191
E7	Clinical Outcome Data	193
APPENDIX I	Key Personnel Requirements	195
APPENDIX II	Cord Blood Unit Labeling	199
APPENDIX III	Accompanying Documents at Distribution	201
APPENDIX IV	Testing Requirements	203
APPENDIX V	Specification Requirements for Cord Blood Units Stored for Clinical Administration	205
ACKNOWLEDGEMENTS		207
INDEX		209
CONTACT INFORMATION		215

This page intentionally left blank.

NetCord-FACT Accreditation Manual

INTRODUCTION

This Accreditation Manual accompanies the *NetCord-FACT International Standards for Cord Blood Collection, Banking, and Release for Administration, Sixth Edition, 2016* (the Standards). The purpose of the manual is to provide guidance to applicants for accreditation and to on-site inspectors. This manual explains the intent and rationale for specific standards, and provides explanations, examples, and alternative approaches that will be helpful in the accreditation process. The intent is to provide examples of practices compliant with Standards, but not to provide an exhaustive list of possible ways to meet the Standards. There are many effective mechanisms by which to achieve compliance with the Standards and by which to inspect applicant Cord Blood Banks.

This manual is organized by the alphanumeric order of the Standards. Each standard is quoted in its entirety, followed by guidance that includes an explanation of the applicable standard(s), ways an applicant may document and an inspector may verify compliance, and examples to illustrate how a standard may be applied. Inspectors are not limited to the methods for verifying compliance described in this manual. This information is intended to inform applicants of the type of evidence inspectors will need to review on-site, and enable applicants to have such evidence readily available to the inspector. Updates are made to this manual periodically as needed. In the event that a printed copy of this manual differs from the version posted on the FACT website at www.factwebsite.org, the web version prevails. In the event of translation into a language other than English, the official version is the English version.

Each edition of the Standards is a collaboration between the International NetCord Foundation (NetCord) and the Foundation for the Accreditation of Cellular Therapy (FACT). Founded in 1997, NetCord is an association of umbilical cord blood banks whose members seek to promote the highest quality in cord blood products, to balance the global supply and demand for umbilical cord blood, and to encourage and facilitate the use of cord blood transplants by promoting laboratory and clinical research and providing professional and public education. FACT was founded in 1996 by its two parent organizations, the American Society for Blood and Marrow Transplantation (ASBMT) and the International Society for Cellular Therapy (ISCT). FACT promotes quality medical and laboratory practice of cellular therapy and regenerative medicine through its peer-developed standards and voluntary inspection and accreditation program.

The major objective of the sixth edition Standards is to promote quality medical and laboratory practices throughout all phases of cord blood collection, banking, and release for administration to achieve consistent production of quality placental and umbilical cord blood units for administration. These Standards cover 1) collection of cord blood cells, regardless of the methodology or site of collection; 2) screening, testing, and eligibility determination of the maternal and infant donor according to Applicable Law; 3) all phases of processing, cryopreservation, and storage, including quarantine, testing, and characterization of the cord blood unit; 4) making the cord blood unit available for administration, either directly or through listing with a search registry; 5) the search process for selection of specific cord blood units; 6) reservation and release of cord blood units for clinical use; and 7) all transport or shipment of cord blood units, whether fresh or cryopreserved. To be compliant with the Standards, Cord Blood Banks must use validated methods; qualify equipment, supplies, and reagents; maintain a comprehensive, properly documented Quality Management (QM) Program; and track the clinical outcomes of patients who receive cord blood units from that bank.

The Standards are limited to the banking of placental and umbilical cord blood for clinical use in related or unrelated recipients, for research, or both. It is not the intent of these Standards to address collection of bone marrow or peripheral blood progenitor cells or alternative types of stem cells, including, but not limited to, embryonic, pancreatic, muscular, or neuronal. For cord tissue storage, these Standards only apply to tissue samples retained for testing and research purposes. Processes for storing cord tissue for therapeutic intent fall under the scope of the *FACT Common Standards for Cellular Therapies*. Standards for the administration of cord blood cells, either allogeneic or autologous, are covered in the *FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration*.

The Standards are developed by consensus, based on the best available evidence-based science to the greatest extent possible, placing emphasis on research on clinical outcomes of cord blood recipients. Cord blood banking is an emerging and evolving field. For those areas where there are little or no definitive data on clinical outcomes relating to a particular standard, the NetCord-FACT Standards Committee weighed the available evidence from preclinical studies and accepted scientific theory.

In the Standards, there is a deliberate and specific use of the terms “shall” and “should.” For purposes of both the Standards and this manual, “shall” is used to indicate that the standard is a requirement and that the standard is to be complied with at all times. The term “should” indicates an activity that is recommended or advised, but for which there may be effective alternatives. An applicant is expected to defend its practice when it deviates from a recommended or advised activity. Wherever there is a discrepancy between the language of the Standards and the guidance in this manual, the term used in the Standards shall prevail.

These Standards are designed to provide minimum guidelines for Cord Blood Banks, facilities, and individuals performing cord blood donor management, collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, and distribution, or providing support services for such procedures. These Standards are not intended to establish best practices or include all procedures and practices that a Cord Blood Bank, facility, or individual should implement if the standard of practice in the community or Applicable Law establish additional requirements. Each Cord Blood Bank, facility, and individual should analyze its practices and procedures to determine whether additional standards apply. Compliance with the Standards is not an exclusive means of complying with the standard of care in the industry or community or with local, national, or international laws or regulations. FACT and NetCord expressly disclaim any responsibility for setting maximum standards and further expressly disclaim any responsibility, liability, or duty to member programs, directors, staff, or program donors or patients for any such liability arising out of injury or loss to any person by the failure of member programs, directors, or staff to adhere to the Standards or related guidance. FACT and NetCord acknowledge that licensure of cord blood banks may be required in some jurisdictions. These Standards and Guidance do not address all licensure requirements of any governmental agency.

ACCREDITATION

The basis for FACT-NetCord accreditation is documented compliance with the current edition of these Standards. Cord Blood Banks are not required to have any specific structure or business model, and may contract services for their operations. However, to be eligible for accreditation, each bank must have processes in place to meet all of the Standards, whether the activities are performed internally or by contract with another facility. FACT and NetCord will not accredit banks wishing only to comply with Standards for portions of the cord blood unit manufacturing process, nor is there a category for FACT-NetCord affiliation. Accreditation is for a Cord Blood Bank’s program, not for specific CB units. If the banking program relocates,

the services at the former location will not necessarily still be accredited, nor does accreditation automatically transfer with the program. Prior to relocation, the accredited Cord Blood Bank will be required to inform FACT and NetCord of its new space, and comply with the requirements to maintain accreditation. Additionally, accreditation does not accompany individual units in the event that inventory is transferred to a different bank.

The inspection and accreditation process includes submission of written documents and an on-site inspection of the Cord Blood Bank, Cord Blood Collection Sites, and Cord Blood Processing and Storage Facilities. Depending on the number of Cord Blood Collection Sites associated with the Cord Blood Bank, all or a subset of the sites will be visited. The inspection team typically includes at least three inspectors and may include interpreters provided by the Cord Blood Bank for banks where English is not the primary language. The FACT-NetCord inspectorate consists of experienced individuals active in the field who have a strong and vested interest in ensuring the availability of the highest quality cord blood units for administration. The inspectorate includes transplant physicians, Cord Blood Bank Directors and Medical Directors, Cord Blood Collection Directors, and Cord Blood Processing Facility Directors. A cord blood bank inspector must be affiliated with a FACT or FACT-NetCord accredited or applicant facility, and must also be an individual member of ASBMT or ISCT, or affiliated with a NetCord member bank. All inspectors must complete an inspector training course, pass a written exam, participate in at least one inspection as a trainee inspector, and participate in ongoing education.

FACT-NetCord accredited Cord Blood Banks are reinspected routinely every three years, or in response to complaints or information that a bank, site, or facility may be non-compliant with the Standards, or as determined by the FACT and NetCord Boards of Directors. Accreditation may be suspended or terminated if a bank, site, or facility fails to comply with the current edition of the Standards.

Accredited cord blood banks and the services provided are listed on the FACT website at www.factwebsite.org.

This page intentionally left blank.

TERMINOLOGY, TENETS, ABBREVIATIONS, AND DEFINITIONS

PART A

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

PART A: TERMINOLOGY, TENETS, ABBREVIATIONS, AND DEFINITIONS

A1 TERMINOLOGY

For purposes of these Standards, the term *shall* means that the Standard is to be complied with at all times. The term *should* indicates an activity that is recommended or advised, but for which there may be effective alternatives. The term *may* is permissive, indicating that the practice is acceptable, but not necessarily recommended.

A2 TENETS

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

- A.2.1 Where applicable laws and regulations include more stringent requirements than these Standards, those laws and regulations supersede the Standards. Conversely, when these Standards are more stringent than applicable laws and regulations, the Standards must be followed.
- A.2.2 Applicant organizations are responsible for providing verifiable documentation of evidence of compliance with these Standards.
- A.2.3 Standards related to services not provided by the applicant do not apply to the applicant organization. The burden to demonstrate that a requirement is not applicable rests with the applicant organization.

A3 ABBREVIATIONS

The following abbreviations are used in these Cord Blood Standards:

<i>ABO</i>	Major human blood group including erythrocyte antigens, A, B, O
<i>AC</i>	Accompany
<i>AF</i>	Affix
<i>ASHI</i>	American Society for Histocompatibility and Immunogenetics
<i>AT</i>	Attach
<i>°C</i>	Degree Celsius
<i>CB</i>	Cord blood
<i>CBB</i>	Cord blood bank
<i>CBC</i>	Complete blood count (Full blood count)
<i>CB unit</i>	Cord blood unit
<i>CFU</i>	Colony forming unit
<i>DNA</i>	Deoxyribonucleic acid
<i>EFI</i>	European Federation for Immunogenetics
<i>FACT</i>	Foundation for the Accreditation of Cellular Therapy
<i>FDA</i>	United States Food and Drug Administration
<i>GVHD</i>	Graft-versus-host disease
<i>HLA</i>	Human leukocyte antigen
<i>HPC</i>	Hematopoietic progenitor cell
<i>HTA</i>	United Kingdom Human Tissue Authority

<i>IRB</i>	Institutional Review Board
<i>ISBT</i>	International Society of Blood Transfusion
<i>µg</i>	Microgram
<i>mL</i>	Milliliter
<i>QM</i>	Quality Management
<i>Rh</i>	Human erythrocyte antigen, Rhesus
<i>Rx</i>	Prescription
<i>TGA</i>	Australia Therapeutic Goods Administration
<i>TNC</i>	Total nucleated cell
<i>USDA</i>	United States Department of Agriculture
<i>WMDA</i>	World Marrow Donor Association

A4 DEFINITIONS

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

Accompany (AC): To go or be together with, but not attached. Information that must accompany the cord blood unit in a sealed package may alternatively be attached or affixed.

Administration: Delivery of a cord blood unit to the recipient (via routes such as infusion).

Adventitious agent: Any extraneous microbiological, chemical, or radiobiological substance introduced into the cord blood unit during collection, processing, or administration.

Adverse event: Any unintended and unfavorable sign, symptom, abnormality, or condition temporally associated with an intervention, medical treatment, or procedure 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 cord blood unit for which there is a reasonable possibility that the cord blood unit caused the response.

Affix (AF): To adhere in physical contact with the cord blood unit container.

Allogeneic: Obtained from an infant donor and intended for administration into a genetically distinct related or unrelated recipient.

Applicable Law: Any local, national, or international statute, regulation, or other governmental law that is applicable to cord blood donor management including recruitment or eligibility, or to cord blood collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, or distribution that is relevant to the location or activities of the Cord Blood Bank, Cord Blood Collection Site, or Cord Blood Processing Facility.

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

Attach (AT): To fasten securely to the cord blood unit 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, Standard Operating Procedures, or operations have been properly implemented and are being followed.

Autologous: Derived from and intended for the same individual.

Available for distribution: The time at which the cord blood unit may leave the control of the facility.

Biohazard legend: The universal biohazard symbol.

Biological product deviation: For unrelated cord blood units, a deviation from Applicable Law, standards, or other established specifications that relate to the prevention of communicable disease transmission or cord blood unit contamination; or an unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease or may lead to cord blood unit contamination. For related cord blood units, a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of the product.

Calibrate: To set measurement equipment against a known standard.

Calibration: Periodic scheduled activity to check and maintain the accuracy against a known standard.

CD34: The 115 kD glycoprotein antigen, expressed by a small portion of cord blood cells, that is defined by a specific monoclonal antibody (anti-CD34) using the standardized cluster of differentiation (CD) terminology. Hematopoietic progenitor cells are largely contained within the CD34 cell population of cord blood units.

Cellular therapy product: A somatic cell-based product, including cord blood, that is procured from a donor and intended for processing and administration.

Circular of information: An extension of container labels that includes handling instructions for the use of the cord blood unit, indications, contraindications, side effects and hazards, dosage, and administration recommendations.

Clinical Program: An integrated medical team that evaluates and administers cord blood units as a source of cells for its patients.

Colony forming unit (CFU): A clonogenic cell able to produce hematopoietic colonies *in vitro* under specific conditions in the presence of appropriate colony stimulating factors and defined by the type of mature progeny that develop.

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

Collection kit: Package of all materials required to collect a single CB unit.

Communicable disease: A disease or disease agent for which there may be a risk of transmission by a cord blood unit either to a recipient or to the people who may handle or otherwise come in contact with the cord blood unit.

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

Complaint: Any written, oral, or electronic communication about a problem associated with a distributed cord blood unit or with a service related to donor management or the collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, distribution, or administration of a cord blood unit.

Contiguous segment: A sealed length of tubing integrally attached to the cord blood unit that contains a sample representative of the cord blood unit that may be used for testing.

Controlled document: A document related to manufacturing of a product or provision of a service that may not be modified or revised without specific approval.

Cord blood (CB): The infant's blood remaining in the placenta and umbilical cord after the umbilical cord has been clamped.

Cord Blood Bank (CBB): An integrated team under a single Cord Blood Bank Director responsible for donor management and the collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, and distribution of cord blood units.

Cord blood banking (CB banking): The processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, and distribution of cord blood units intended for administration.

Cord blood collection: The procurement of cord blood for banking and administration before and/or after the placenta is delivered.

Ex utero: The collection of cord blood cells from the placental or umbilical cord vessels after the placenta has been delivered.

In utero: The collection of cord blood cells from the placental or umbilical cord vessels after the infant donor has been delivered and separated from the umbilical cord, but before the placenta has been delivered.

Cord Blood Collection Site: The location where the infant donor is delivered and the cord blood unit is collected.

Fixed Cord Blood Collection Site: A collection site where there is a written agreement between the collection site and the Cord Blood Bank for the collection of cord blood units over time. The agreement shall describe the interaction between the Cord Blood Collection Site and the Cord Blood Bank for all aspects of the collection process including, at a minimum, personnel training, record keeping, collection, storage, and transportation or shipping of a cord blood unit.

Non-fixed Cord Blood Collection Site: A collection site where the collection of cord blood is initiated by the infant donor's mother or family, with documentation that a health care professional has agreed to perform the collection in accordance with the Cord Blood Bank collection procedures and has training that covers each aspect of the collection process.

Cord Blood Processing Facility: The location where cord blood processing activities are performed in support of the Cord Blood Bank. A Cord Blood Processing Facility may be part of the same institution as the Cord Blood Bank or may be part of another institution and performs these functions through contractual agreement.

Cord blood unit (CB unit): The nucleated cells including stem and hematopoietic progenitor cells harvested from placental and umbilical cord blood vessels from a single placenta after the umbilical cord has been clamped. Unless otherwise specified, the term cord blood unit in this document refers to any cord blood unit regardless of method of collection or intended use.

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

Critical procedure: A process or procedure that has the potential to directly impact the quality, safety, identity, purity, or potency of the cellular therapy product or service.

Cryopreservation: The processing of viable cells or tissues that consists of cooling the product to a very low temperature where viability is maintained.

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

Deviation: The action of departing from an established course or accepted standard.

Unplanned Deviation: Occurred without intent.

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

Disposition: The current status, location, or use of a cord blood unit.

Distribution: Any transportation or shipment (including importation and exportation) of a cord blood unit that has been determined to meet all applicable release criteria or urgent medical need requirements.

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

Infant donor: The infant from whose placenta or umbilical cord the cord blood is obtained.

Maternal donor: The mother who carries the infant donor to delivery. This may be the genetic or surrogate mother.

Unrelated donor: The infant donor whose cord blood is collected and stored for use by a person with no known genetic relationship.

Related donor: The infant donor whose cord blood is collected and stored for autologous use by the donor or for allogeneic use by a genetically related recipient.

Donor screening: The process of identifying risk factors for transmissible disease through review of a current donor medical history interview (to include high-risk behaviors), physical examination results, and other medical records.

Donor suitability: The maternal and infant donor's medical fitness to undergo the cord blood collection procedure.

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: An allogeneic infant donor or maternal donor for whom all the donor screening and testing have been completed in accordance with Applicable Law and who has been determined to be free of risk factor(s) for relevant communicable diseases.

Engraftment: The reconstitution of hematopoiesis or other cellular functions with cells from a donor.

Errors and accidents: Any unforeseen or unexpected deviations from Applicable Law, these Standards, or other established specifications that may affect the safety, purity, or potency of a cord blood unit.

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

First-degree relatives: A family member who shares approximately 50 percent of his/her genes with a particular family member. First-degree relatives include parents, siblings, and offspring.

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 (marrow, umbilical cord blood, peripheral blood, or other tissue source).

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

High resolution typing: Determination of a set of alleles that encode the same protein sequence for the region of the HLA molecule called the antigen binding site and that excludes alleles that are not expressed as cell-surface proteins. The antigen binding site includes domain 1 and domain 2 of the class I α polypeptides, and domain 1 of the class II α and domain 1 of the class II β polypeptide chains.

Identifier: A numeric or alphanumeric sequence used to differentiate one item from another like item.

Incomplete donor eligibility: An infant or maternal donor for whom the donor eligibility has not been completed in accordance with all donor screening and testing required by Applicable Law.

Indefinitely: A timeframe without a fixed or specified limit.

Ineligible: An infant or maternal donor for whom all the donor screening and testing has been completed in accordance with Applicable Law and who has identified risk factor(s) for relevant communicable diseases.

Institutional Review Board (IRB) or Ethics Committee: A Board or Committee established by an institution in accordance with Applicable Law 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. ICCBBA, Inc. (www.iccbba.org) is the organization charged with the international maintenance of this database.

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

Licensed health care professional: An individual certified by the applicable governmental agency to be competent for the duties performed.

Linkage: The maintenance of basic demographic information, including name, that would allow tracing of a cord blood unit to the identification of the infant donor and the mother.

Listing: The process of transferring information about a cord blood unit to be available for search.

Low resolution typing: A DNA-based typing result at the level of the digits comprising the first field in the DNA-based nomenclature. Examples include A*01; A*02. If the resolution corresponds to a serologic equivalent, this typing result shall also be called low resolution.

Manipulation: *Ex vivo* procedure(s) that alter(s) the cord blood unit.

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

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

Unmanipulated: Cord blood as obtained at collection and not subjected to any form of processing.

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

May: Acceptable but not necessarily recommended.

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

Monitoring: Recording quality parameters or indicators on a regular basis.

Mother: Any of the following:

Birth mother: The woman who carries the infant donor to its delivery; may be the genetic mother or a surrogate mother.

Genetic mother: The woman from whose egg the infant donor develops; the egg donor.

Mother: When used unmodified, the term mother refers to the mother who is both the genetic and birth mother.

Surrogate mother: The woman who carries an infant donor not genetically her own from an embryo to delivery. Under circumstances of a surrogate mother carrying the infant donor to term and the cord blood unit being collected, both the surrogate and the genetic mother shall be considered for purposes of communicable disease screening and testing; the genetic mother shall be considered for purposes of genetic information.

Negative selection: The manipulation of cord blood such that a specific cell population(s) is depleted.

Nonconforming cord blood unit: Any cord blood unit that does not completely meet the requirements specified by these Standards, the Cord Blood Bank, or Applicable Law.

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 at all times to all cord blood unit containers.

Policy: Document that explains how the goals of the organization will be achieved or serves as a means by which authority can be delegated.

Positive selection: The manipulation of cord blood such that a specific cell population(s) is enriched.

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

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, packaging, and labeling cord blood units, including microbial testing, preparation for storage, and removal from storage. For the purpose of these Standards, processing does not include collection, donor screening, donor testing, cryopreservation, storage, or distribution.

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

HPC, Cord Blood: A cell product containing hematopoietic progenitor cells obtained from cord blood.

NC, Cord Blood: A cell product containing nucleated cells obtained from cord blood.

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

MSC, Cord Blood: A cell product containing mesenchymal stromal cell derived from cord blood.

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

Protocol: A written document describing steps of a treatment or 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 equipment, supplies, and reagents function consistently within established limits.

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

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

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

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 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 cord blood units, including testing and product release.

Quality handbook: A document describing the application of general principles of quality management in cord blood banks using templates, scenarios, and sample documentation. It is an adjunct to help cellular therapy programs prepare for and maintain FACT-NetCord accreditation. May also be referred to as a quality guide or manual.

Quality improvement: The actions, planned and performed, to develop a system to review and improve the quality of a product or process.

Quality management (QM): 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 cord blood unit or increase the risk of communicable disease introduction or transmission.

Quality Unit: Personnel with responsibility for and authority to approve or reject in-process materials, all components, cord blood unit containers, closures, packaging material, labeling, and cord blood units.

Quality Unit Manager: A qualified individual who establishes methods to review, modify, approve, and implement all Standard Operating Procedures related to Quality Management and to monitor compliance with these Standards.

Quarantine: The segregation of a cord blood unit to prevent cross-contamination or improper release. Quarantine can be temporal, physical, electronic, or a designation within the cord blood unit record.

Recipient: The individual into whom the cord blood unit was administered.

Registry: An organization that publishes or makes available the description of cord blood units available for administration and may conduct searches of the available cord blood units, either exclusively or in conjunction with the Cord Blood Bank as defined in their agreement.

Release: The removal of a cord blood unit from quarantine or in-process status when it meets specified criteria.

Reservation: A temporary allocation of a cord blood unit to a specific recipient to prevent consideration of that cord blood unit for another recipient.

Rh: The abbreviation for the Rhesus system of human red cell antigens; is used in this document to refer to the Rh (D) antigen only unless otherwise specified.

Root cause analysis: A method of problem solving used for identifying the underlying factors that contributed to the issue. Contributing factors shall be identified. Asking questions assists in identifying the root cause.

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

Sample: Biological material used for testing. When unmodified, refers to all applicable samples.

Associated sample: Birthing tissue (e.g., cord tissue, Wharton's Jelly) derived from the infant donor or maternal donor.

Maternal sample: Aliquot of cells, plasma, serum, or cellular material from the blood of the mother.

Reference sample: Aliquot of cells, plasma, serum, or cellular material from the cord blood unit, the umbilical cord, or the placenta stored for future analysis of product identity, potency, quality, purity, tissue typing, or infectious disease testing, should the need arise, after banking of the cord blood unit.

Representative sample: Aliquot of the final cord blood product that is stored under the same conditions as the cord blood unit, and can be used to test for viability, potency, or stability.

Retention sample: Aliquot of the final cord blood unit saved for future use, such as investigating adverse events or retroactive quality control activities.

Search: The process used to produce a report of cord blood units that are potential matches for a recipient.

Selection: The process of identification of a donor or cord blood unit according to defined criteria.

Shall: To be complied with at all times.

Shipping: The physical act of transferring a cord blood unit within or between facilities during which the unit leaves the control of personnel trained by the distributing or receiving facility.

Should: Recommended or advised, but effective alternatives may exist.

Standard Operating Procedure: Written detailed instructions required to perform a procedure.

Standard Operating Procedures Manual: A compilation of the current Standard Operating Procedures.

Standards: The current edition of the *International Standards for Cord Blood Collection, Banking, and Release for Administration* published by NetCord and FACT.

Sterility testing: The processes used to screen for the presence of microbial agents.

Storage: Holding cord blood units for future processing or distribution.

Time of collection: The time of day that the cord blood collection is completed.

Total nucleated cell (TNC) count: The number of cells with a nucleus or nuclei in a cord blood unit.

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 administration of allogeneic or autologous cord blood cells with the intent of providing transient or permanent engraftment in support of therapy for disease.

Transport: The physical act of transferring a cord blood unit within or between facilities. During transportation the product does not leave the control of personnel trained by the transporting or receiving facility.

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

Unique identifier: A numeric or alphanumeric sequence used to designate a specific cord blood unit with reasonable confidence that the identifier will not be used for another purpose, including for another cord blood unit.

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 cord blood unit.

Validation: Confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled.

Variance: A deviation from recommended practice or Standard Operating Procedure.

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

Verification typing: HLA typing performed on an independent sample (or, for a cord blood unit, from an attached segment or from the unit itself) with the purpose of verifying concordance of that typing assignment with the initial HLA typing assignment. Concordance does not require identical levels of resolution for the two sets of typing but requires the two assignments to be consistent with one another.

Viability assessment: The determination of the proportion of living cells using dye exclusion, flow cytometry, or progenitor cell culture methods.

Warming event: Any event when a cryopreserved cord blood unit reaches -150°C or warmer during the life of the cryopreserved cord blood unit.

Written: Documentation in human readable form.

**These definitions are as of publication. The current terminology in Chapter Three of the ICCBBA document, "ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions," is required. This document can be found at <http://www.iccbba.org> > Subject Area > Cellular Therapy > Standard Terminology.*

This page intentionally left blank.

CORD BLOOD BANK OPERATIONAL STANDARDS

PART B

- B1 General Requirements
- B2 Quality Management
- B3 Policies and Standard Operating Procedures
- B4 Facilities and Safety
- B5 Cord Blood Bank Operations
- B6 Coding and Labeling of Cord Blood Units
- B7 Equipment
- B8 Supplies and Reagents
- B9 Inventory Management
- B10 Inventory Transfer
- B11 Documents and Records Requirements
- B12 Interruption of Operations at Established Sites

PART B: CORD BLOOD BANK OPERATIONAL STANDARDS

B1: GENERAL REQUIREMENTS

STANDARD:

B1.1 The Cord Blood Bank (CBB) shall consist of an integrated team responsible for donor management; collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, and distribution of cord blood (CB) units; and recipient follow-up.

Explanation:

The Cord Blood Bank (CBB) is an inclusive program that is responsible for the entire process from donor recruitment to cord blood (CB) unit distribution, with outcome analysis. If there are shared responsibilities among multiple organizations, it is the responsibility of the CBB to require all parties involved to be in compliance with these Standards as they pertain to the shared responsibilities.

The Standards apply to CB units collected for related use (autologous or related allogeneic) and unrelated allogeneic use. Related use includes those units for which there is a known recipient or family. Unrelated use is a donation to a CBB from which transplant physicians can select a unit based upon its suitability for a recipient unrelated to the donor.

If a standard does not specify the type of donation, it applies to both unrelated and related CB units. **Figure 1: Specified Requirements for Unrelated and Related Cord Blood Units** outlines standards that are specifically for unrelated or related CB units to assist CBBs with understanding when a standard may or may not apply depending on their business models. Standards that apply to both unrelated and related CB units are not included in this table, nor are the differences in the requirements included in the appendices.

Figure 1: Specified Requirements for Unrelated and Related Cord Blood Units

Subject	Unrelated CB Units	Related CB Units
Return of CB Units to Inventory	B9.5.1, E6.5	B9.5.2
Informed Consent	C4.6	C4.7
History of Genetic or Malignant Disease	B5.5.4.2	
Ineligible CB Units		C5.1.3
<i>In utero</i> Collection	C6.2.2	
CB Acceptance Criteria	D3.1.2	D3.1.3, D3.1.4
Cryopreservation	D3.2.6	D3.2.7
Warming Events	D6.5.2.2	
CB Unit Disposal	D8.4.2.1	C4.5.12.2, C4.5.12.3, D8.4.2.2, D8.4.3
Microbial Cultures	D9.3.2.1	D9.3.2.2
CB Unit Listing	B1.3, E1.2.2, E1.4, E1.5, E1.6, E2.2	E1.3
Data for Clinical Program		E3.3.2, E3.3.4.2
Discontinuation of Banking		B12.3.6

STANDARD:

B1.2 The CBB, each CB Collection Site, and each CB Processing Facility shall operate in compliance with Applicable Law and these Standards.

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

Example(s):

CB units manufactured in the U.S. or intended for use in the U.S. are all regulated by the current Good Tissue Practices in 21 CFR 1271, but will also be subject to one of the following sets of regulations:

- Section 361 of the Public Health Services (PHS) Act (related CB units),
- Section 351 of the PHS Act (unrelated allogeneic CB units under IND), and/or
- 21 CFR Part 601 (minimally manipulated, unrelated CB units intended for hematopoietic reconstitution for specified indications under a biologics license application (BLA)).

The FDA published two guidance documents regarding minimally manipulated, unrelated allogeneic CB units. One discusses BLAs and the other discusses minimally manipulated, unrelated allogeneic CB units that do not meet licensure requirements. These documents can be found at

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm>.

In other countries, such as Australia, CB is a licensed product and different governmental regulations apply.

STANDARD:

B1.3 The CBB shall have a mechanism to list and distribute unrelated CB units for clinical use.

B1.3.1 If the CBB utilizes a registry to provide services related to the listing, search, selection, reservation, release, or distribution of a CB unit:

B1.3.1.1 The responsibilities of the registry shall be clearly documented.

B1.3.1.2 The registry shall comply with these Standards as applicable to its responsibilities.

B1.3.1.3 The registry should be accredited by the WMDA.

B1.4 If the CBB contracts with any other entity for services related to CB unit donor management, collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, distribution, or any other aspect of banking, the responsibility of each entity shall be clearly documented in a written agreement.

B1.4.1 Each contracted entity shall comply with these Standards as applicable to its responsibilities.

Explanation:

The Standards are not intended to dictate specific CBB structures or business practices. Processing and/or collection services may be contracted with other services as desired as long as the responsibilities of each service are well documented. Accreditation by FACT-NetCord; however, does require that the CBB use

collection, banking, and release for administration services that meet the Standards. There is no partial accreditation for these services individually; each entity performing all or part of these services must be inspected in relation to their activities with the CBB.

Part B of these Standards pertains to the entire CBB and each of its CB Collection Sites and CB Processing Facilities.

Evidence:

If a CBB works with a registry or external facility that performs specified functions, the responsibilities of each must be clearly outlined in a written agreement.

Documentation that entities performing donor management, collection, processing, cryopreservation, and storage meet the Standards requires successful completion of an on-site inspection. Registries used by the CBB should be accredited by the WMDA.

STANDARD:

B1.5 There shall be a CBB Director, a CBB Medical Director, a CB Collection Director, a CB Processing Facility Director, and a Quality Unit Manager as outlined in the Key Personnel Requirements table in Appendix I.

Explanation:

The CBB may choose to have a single individual fulfill more than one of these key roles; however, the Quality Unit Manager must not be the same person as the CBB Director, CBB Medical Director, CB Collection Director, or CB Processing Facility Director. The Quality Unit Manager may not report to anyone in operations, though strong working relationships must exist to meet the intent of the Standards.

No matter how a CBB chooses to fill these positions, the individuals must meet the required qualifications. For example, if one person serves as both the CBB Director and the CB Processing Facility Director, he/she must have the training required for both of these positions.

STANDARD:

B1.5.1 The CBB shall have an adequate number of qualified staff for its operations.

Explanation:

The CBB must specify what constitutes qualified staff. B2.5 lists details regarding personnel requirements.

STANDARD:

B1.6 Claims made in educational, promotional, or recruitment materials shall be supported by scientific evidence.

Explanation:

CBBs have a responsibility to prospective donors to truthfully state the benefits of CB banking. Scientific evidence does not need to be detailed in advertisements, but the CBB must only state claims of clinical efficacy that is supported by such evidence.

Evidence:

If advertisements make claims not widely supported in published literature, the CBB must provide the inspector with scientific evidence supporting the inclusion of the information in donor recruitment materials.

B2: QUALITY MANAGEMENT

STANDARD:

B2.1 There shall be a QM Program that incorporates all key CBB functions.

B2.1.1 There shall be a Quality Unit that has responsibility for ensuring the QM Program is effectively established and maintained.

Explanation:

As defined in these Standards, the "Quality Unit" includes all personnel with responsibility and authority to approve or reject CB units. The structure of this unit may vary according to applicable regulations and licensure status of the bank.

Due to increasing licensure requirements around the world, CBBs must have an independent Quality Unit to approve CB units for release. This unit must not replace medical review, which is necessary to adequately consider the medically relevant characteristics of the CB unit in terms of its intended use. However, the independent review is intended to provide a final, unbiased check for quality.

There must be a designated person to oversee the QM Program. The CBB Director and Quality Unit Manager must both be active participants in establishing, maintaining, and implementing the program. This includes reviewing key performance data across collection, processing, release for administration, and clinical outcomes.

Quality Unit Managers typically come from a variety of backgrounds and are not required to have QM training within a specific field. On-site QM training is also acceptable.

Day-to-day tasks of the QM Program, such as the performance of audits, may be delegated to an individual within the CBB with sufficient expertise. The designated person must have sufficient knowledge and training to adequately perform the delegated functions.

Example(s):

A designee for QM activities can be a member of another department, such as an institutional Quality Assessment and Improvement Department, who devotes some time to the QM activities of the CBB, or he/she could be a member of CBB personnel. The staff conducting the quality assessment audits may be the designated manager or another staff member, but it must not be the staff member who performed the work under review, unless performed in a retrospective fashion with enough delay between the time the work was performed and the time it is audited to mitigate bias.

STANDARD:

B2.1.1.1 The Quality Unit shall have a reporting structure independent of CB unit manufacturing.

Explanation:

CBBs must minimize conflicts of interest of the Quality Unit as required by Applicable Law. While the Quality Unit Manager may still be employed by the CBB, he/she should be independent of the CB unit manufacturing process (including collection, processing, and storage) to maintain objectivity during the review of unit records and approval for release.

Quality Units provide an objective review of CB units and operations, unbiased by work performed themselves. Although this review is independent, the Quality Unit must still have regular interaction with the CBB Director and CBB personnel, and provide regular updates and information related to the performance of the QM Program.

STANDARD:

B2.1.1.2 The Quality Unit Manager shall not have oversight of his/her own work if this person also performs tasks in the CBB.

B2.2 The CBB shall establish and maintain a written QM Plan that describes the QM Program.

Example(s):

QM Plans can be approached and formatted in a number of ways. For instance, a CBB may outline its plan according to the FDA's GTPs or GMPs, an ISO system format, or according to these Standards. Regardless of the format selected, the CBB needs to demonstrate that all key areas of QM are addressed. If any components of the CBB's plan are part of a larger entity's program, e.g., occupational health and safety training, the CBB must demonstrate that the records of training and results of evaluations are referred back to the CBB.

STANDARD:

B2.3 The QM Plan shall summarize and reference documentation of the relationship and interaction among all participating facilities and services, including, at a minimum, CB Collection Sites, CB Processing Facilities, information technology services, testing laboratories, storage facilities, registries, and outcomes databases.

B2.3.1 The QM Plan shall summarize and reference an organizational chart of key positions, functions, and interactions within the CBB, the CB Collection Sites, and the CB Processing Facility.

Example(s):

In addition to an organizational chart, a description of how key personnel interact to implement QM activities is particularly useful for non-fixed CB Collection Sites, or those sites not staffed by CBB personnel, where the lines of communication may not be as clear as in CBBs who staff their own CB Collection Sites.

STANDARD:

B2.4 The QM Plan shall summarize and reference policies and Standard Operating Procedures for establishment and maintenance of written agreements with external parties whose services impact the CB unit.

B2.4.1 Agreements shall include the responsibility of the external party performing any relevant aspect of donor screening and testing, CB collection, processing, testing, storage, or distribution for administration to comply with Applicable Law, these Standards, and the requirements of other applicable accrediting agencies.

B2.4.2 Agreements shall be dated and reviewed on a regular basis.

Explanation:

Written agreements are required for individuals or organizations that are external to the CBB but perform services that impact CB units. This is different from designees, who are typically personnel within the CBB who have been delegated responsibilities for which they have the appropriate training and expertise.

Example(s):

If the HLA typing review is the responsibility of a registry, the CBB must outline this in a written agreement; if the HLA typing is delegated to the CB Processing Facility Director because he/she has the necessary training and expertise, a written agreement is not required.

STANDARD:

B2.5 The QM Plan shall summarize and reference policies and Standard Operating Procedures addressing personnel requirements, training, and competency assessment for each position in the CBB. Personnel requirements shall include at a minimum:

Explanation:

These personnel requirements are intended for key personnel who perform tasks related to the actual CB units. Clerical staff is not required to meet these requirements.

STANDARD:

B2.5.1 A current job description for each position.

B2.5.2 A system to document the following for all staff:

B2.5.2.1 Initial qualifications.

B2.5.2.2 New employee orientation.

Explanation:

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

STANDARD:

B2.5.2.3 Initial training for all procedures performed.

B2.5.2.4 Annual assessment of competency.

B2.5.2.5 Continuing education.

B2.5.2.6 Personnel identifier.

Explanation:

A personnel identifier is a mechanism to uniquely identify a person and determine who completed a task. Therefore, the identifier should match the manner in which personnel sign documents.

Example(s):

Examples include initials, barcode, or employee number; basically the identifier should reflect the manner in which personnel sign documents.

STANDARD:

B2.5.3 A system that provides consistent training programs.

B2.5.4 A description of minimum trainer qualifications.

Explanation:

CB banking is a specialized field and there will not often be relevant “train-the-trainer” courses available to allow personnel to become qualified as trainers of new staff members. The QM Plan should describe how CBB personnel become qualified to act as trainers.

Evidence:

The criteria for selection and training of trainers should be clearly defined.

Example(s):

Trainer requirements may be based on experience and continued demonstrated competency, and may also include formal training using external courses.

STANDARD:

B2.6 The QM Plan shall summarize and reference policies and Standard Operating Procedures addressing change control that include at a minimum:

B2.6.1 A description of the proposed change.

B2.6.2 Analysis of the change for compliance with these Standards and Applicable Law.

B2.6.3 Identification of risks of the change to the donor, CB unit, or recipient.

B2.6.4 Determination of impact on existing processes, policies, and Standard Operating Procedures.

- B2.6.5 *Assessment of the need to verify or validate the change.*
- B2.6.6 *System for change approval and effective date.*
- B2.6.7 *Methods for communication of the change and training, if applicable.*
- B2.7 *The QM Plan shall summarize and reference policies and Standard Operating Procedures addressing document control that include at a minimum:*
 - B2.7.1 *The following documents shall be controlled at a minimum:*
 - B2.7.1.1 *Policies and Standard Operating Procedures.*
 - B2.7.1.2 *Worksheets.*
 - B2.7.1.3 *Forms.*
 - B2.7.1.4 *Labels.*
 - B2.7.1.5 *Educational, promotional, and recruitment materials.*

Explanation:

This standard primarily addresses the need for a comprehensive document control system that covers all of the critical documents used by the CBB. The types of documents listed in the standard are what minimally must be included in the document control system; however, CBBs should review their document management system to identify if other documents should also be included, such as work instructions and checklists.

The document control process may be electronic or paper-based. Commercial document control software may be used to streamline this process. These systems can be configured to automatically assign a unique document identifier and version number. Initial approval, document receipt, and records of reading or training may be captured by electronic signatures.

If educational, promotional, and recruitment materials are online, such as online publications, they must be controlled. Any scientific information must be current and supported by scientific evidence. A website should be controlled under the CBB Director's responsibility.

STANDARD:

- B2.7.2 *A procedure for preparation, approval, implementation, review, revision, and archival of all controlled documents.*
- B2.7.3 *A procedure for document approval, including the approval date, signature of approving individual(s), and the effective date.*
- B2.7.4 *A procedure for document distribution to relevant personnel, including acknowledgement of receipt.*

Explanation:

Rather than the implementation of a document being dependent on all staff reading and acknowledging the document, this standard should be interpreted to suggest that a task cannot be performed by personnel until they are trained. In other words, a policy may be implemented before all staff have been trained. Minor revisions, such as grammatical and spelling modifications that do not warrant entirely new versions, may not require retraining of staff.

Evidence:

Signatures to indicate reading and training should be maintained for all new and revised SOPs. This is especially important in CBBs where the central facility manages separate CB Collection Sites. Electronic signatures may be acceptable so long as they can be produced for inspection. Information regarding electronic record systems can be found in B11.

STANDARD:

B2.7.5 Assignment of a numeric or alphanumeric identifier and title to each document and document version regulated within the system.

Explanation:

There must be a listing of active critical documents, including all critical documents that are currently in effect. Documents in electronic format should follow the described document control process of the CBB.

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. There must be processes for the creation, initial review/approval, and implementation/training of each document. The document control system should be designed to track document versions, and include a formal review and approval process for new documents and versions.

Example(s):

Document identifiers and version identifiers may be present in the header or footer of controlled documents. An approval section and the signature of the approving individual may be part of the document (i.e., SOPs), or linked to the controlled document through its identifier (i.e., labels) on another form.

STANDARD:

B2.7.6 A system to protect documents from accidental or unauthorized modification.

B2.7.7 A system for document creation, assembly, review, storage, archival, retention, and retrieval.

B2.7.7.1 There shall be a standardized system for denoting the date each document became effective and when it was archived, if applicable.

B2.7.7.2 There shall be a system for the retraction of obsolete documents to prevent unintended use.

B2.7.7.3 There shall be records of archived documents in their historical sequence.

Explanation:

There must also be a documented system for the use, assembly, storage, archival, and retrieval of documents. Archiving is specifically mentioned in this standard and is an important element of the QM Program. If outcomes change over time, one needs to be able to go back to previous versions of policies, procedures, and forms to determine if an operational change is the cause.

Evidence:

The document control policy or procedure must meet these minimal criteria and there must be evidence that personnel follow the process. The inspector can confirm the effectiveness of the document control by tracing a controlled document (e.g., a form or SOP) from initial creation, through the proposal, approval, review, implementation of revisions or new versions, and archival. The written change control policy or procedure must be effective to prevent unintended changes to processes, policies, or procedures.

The CBB must be able to show previous versions of a procedure that has been revised or replaced. Such archived procedures must be clearly marked in such a manner that they reflect the status of the procedure.

Example(s):

Electronic documents can be protected from inadvertent change by several methods, including using the security features of word processing or spreadsheet program software to lock specific areas or the use of protected Portable Document Format (PDF). The intervals for periodic review may be set globally and automated reminders sent to relevant personnel via email. These systems can generally capture the review date and outcome and also requests for changes to documents.

STANDARD:

B2.8 The QM Plan shall summarize and reference policies and Standard Operating Procedures to support management of electronic record systems and electronic records and to maintain pertinent electronic records, if applicable.

B2.9 The QM Plan shall summarize and reference policies and Standard Operating Procedures for actions to take in the event the CBB's operations are interrupted.

Explanation:

There should be policies and procedures that address interruption in collection or processing due to equipment failure (such as for the handling and labeling of CB units), and also policies and procedures that prevent subsequent delay in collections or processing, such as an additional machine for back up or appropriate alternative arrangements.

There should be policies and procedures in the event that any collection or processing function is discontinued for a period exceeding six months in accordance with Standard B12.

STANDARD:

B2.10 The QM Plan shall summarize and reference policies and Standard Operating Procedures for maintaining confidentiality.

- B2.11 *The QM Plan shall summarize and reference policies and Standard Operating Procedures for the management of internal and external audits and inspections of the CBB.*
- B2.11.1 *There shall be a schedule for conducting audits of key CBB functions annually at a minimum to verify compliance with elements of the Quality Management Program and operational policies and procedures.*
- B2.11.2 *Audits shall be conducted by an individual with sufficient expertise to identify problems, but who is not solely responsible for the process being audited.*
- B2.11.3 *Internal audits shall include at a minimum:*
- B2.11.3.1 *Audit of records and assessment of record review to identify recurring problems, potential points of failure, or need for process improvement.*
- B2.11.3.2 *Audit of external facilities that perform critical contracted services to verify that these facilities have met the requirements of the written agreements.*
- B2.11.4 *The results of audits shall be used to recognize problems, detect trends, identify improvement opportunities, implement corrective and preventive actions when necessary, and follow-up on the effectiveness of those actions.*
- B2.11.5 *Audit results shall be shared with the appropriate Director and/or Medical Director, Quality Unit Manager, manager of the area audited, and other relevant staff.*
- B2.11.6 *There shall be a Standard Operating Procedure for the management of external audits and inspections of the CBB.*
- B2.11.6.1 *Documentation of results of inspection and accreditation visits shall be maintained indefinitely.*

Explanation:

An audit is a documented, independent inspection and review of an establishment's activities, performed according to procedures to verify the degree of compliance by examination of objective evidence. Audits should focus on key functions and may also be prompted in response to observed trends or occurrences (and also designed to detect them). Audits should be scheduled on the basis of the importance of the activity to the quality of the product or service.

Internal audits of key functions include donor management, collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, distribution, and outcome analysis. The entire process for each of these key functions does not need to be included in an individual audit. The CBB may choose to pick one step in a process to audit one year, and another step in the same process to audit the next year.

Each external facility does not have to be audited annually, nor do audits have to be onsite unless required by Applicable Law. It is important to prioritize and focus on the high-risk steps in the process.

Evidence:

CBBs shall provide evidence of a written audit schedule, audit results, actions taken, and follow-up assessments and audits. Review of audit schedules and results is intended to verify an adequate audit process, but it is not the intent to use a facility's audits to identify deficiencies during an inspection.

Example(s):

Examples of ways to audit external facilities include:

- Desk audits using documentation submitted by the external facility,
- Questionnaires to be completed by the external facility,
- Review of performance indicators (e.g., timeliness, accurate reporting, quality results, etc.), and
- On-site audits.

STANDARD:

B2.12 The QM Plan shall summarize and reference policies and Standard Operating Procedures addressing errors, accidents, biological product deviations, adverse events, variances, and complaints, including the following activities at a minimum:

Explanation:

For errors, accidents, biological product deviations, adverse events, variances, and complaints, the CBB must detect, investigate, determine root cause, document, track, evaluate, report, and correct the issues. Adverse events include severe adverse events during administration of the CB unit.

STANDARD:

B2.12.1 Detection.

B2.12.1.1 There shall be a defined process that includes policies or procedures for the recognition and documentation of all issues that require corrective action.

Explanation:

Reviews must include evaluation of both aggregate data and individual records. Common control points are the time of transfer from quarantine to long-term storage or at time of listing the CB unit on registries. Key steps to be reviewed include, for example, donor screening and testing, collection procedure, processing, freezing curve, warming events, and post freeze testing.

STANDARD:

B2.12.2 Investigation.

B2.12.2.1 A thorough investigation shall be conducted by the CBB in collaboration with the involved parties.

B2.12.3 Documentation.

B2.12.3.1 Cumulative files of errors, accidents, biological product deviations, adverse events, variances, and complaints shall be maintained.

Explanation:

Details of errors, accidents, biological product deviations, adverse events, variances, and complaints must be compiled in a cumulative file to use for tracking and trending and be linked to the CB unit record.

The FACT definition of a complaint is "Any written, oral, or electronic communication about a problem associated with a distributed cord blood unit or with a service related to donor management or the collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, distribution, or administration of a cord blood unit." It is important that there be documentation of investigation of all complaints.

Evidence:

Files of errors, accidents, biological product deviations, adverse events, and complaints must be available for inspector review. It is not the intent to use a CBB's adverse reactions, errors, accidents, biological product deviations, or complaints to identify deficiencies during an inspection.

Example(s):

A complaint file is specifically required by 21 CFR 1271 for U.S. CBBs.

STANDARD:

B2.12.3.2 A written report of the investigation including conclusions, follow-up, and corrective action, if applicable, shall be prepared, linked to the record for that final CB unit, and maintained in the applicable cumulative file.

B2.12.3.3 Investigation reports shall be reviewed and approved by the CBB Director or designee.

B2.12.4 Tracking.

B2.12.4.1 Errors, accidents, biological product deviations, adverse events, variances, and complaints shall be tracked and trended to categorize and identify system problems and initiate corrective action.

B2.12.5 Evaluation.

B2.12.5.1 Planned deviations shall be pre-approved by the appropriate CBB Director and/or Medical Director, the Quality Unit, and other staff as appropriate.

B2.12.5.2 Unplanned deviations and associated corrective action, if necessary, shall be reviewed by the appropriate CBB Director and/or Medical Director, the Quality Unit, and other staff as appropriate.

B2.12.5.3 The CBB Director or designee and the Quality Unit shall review all errors, accidents, biological product deviations, adverse events, variances, and complaints in a timely manner. This review shall be documented.

Evidence:

In all cases of errors, accidents, biological product deviations, adverse events, and complaints, documentation must be linked to the CB unit record and be signed off by the CBB Director and Quality Unit, and the information must be relayed to the appropriate individuals.

Example(s):

Some events are unexpected, such as the temperature in a refrigerator that stores reagents climbing slightly out of range. Some events are expected, when one knowingly does not follow a procedural step. An example of the latter may be a CBB choosing to process an autologous donation that arrives outside of the time window described in the SOP due to an unavoidable delay in transport.

STANDARD:

B2.12.5.4 Each complaint shall be evaluated to determine if the complaint is related to a product deviation or adverse reaction.

B2.12.6 Corrective action.

B2.12.6.1 Corrective action shall be implemented and documented as indicated, including both short-term action to address the immediate problem and long-term action to prevent the problem from recurring.

B2.12.6.2 Documentation of the corrective action shall include the nature of the problem requiring corrective action, the impact on the CB Unit, and the identity and disposition of the affected CB unit, if indicated.

B2.12.6.3 Documentation of the corrective action shall be maintained, including the dates of corrective action and a designated timeframe at which the outcome of the corrective action shall be evaluated.

B2.12.6.4 Corrective actions shall be evaluated by the appropriate Director and/or Medical Director or designee, the Quality Unit, and other staff as appropriate.

Explanation:

Corrective action is usually initiated in response to internal or external audits or errors, accidents, biological product deviations, adverse events, or complaints. A corrective action plan should be designed to further investigate or determine the root cause of the event, or trend any possible effect on product quality. Preventive action should be initiated where appropriate to eliminate the likelihood of a future occurrence of the issue. Preventive action is proactive rather than reactive. Corrective and preventive action plans and follow up must be documented.

Example(s):

Corrective action plans may be initiated due to one specific event or for a series of events where an undesirable or unexpected trend is noted.

STANDARD:*B2.12.7 Reporting.*

B2.12.7.1 When it is determined that the CB unit was responsible for an adverse reaction, the reaction and results of the investigation shall be reported to the Clinical Program, other facilities participating in the manufacturing of the CB unit, registries, and governmental agencies as required by Applicable Law or these Standards.

Explanation:

Severe or unexpected events or reactions must be documented, including the investigation, conclusions, follow-up, and corrective action. Each CBB should define adverse events and reactions according to the regulations and standards pertaining to its location and activities.

If there is a reasonable possibility that the reaction may have been caused by the CB unit, the reaction report and investigation results may need to be reported to governmental or granting agencies, IRBs, and registries as required by institutional requirements, law, or standards.

When reporting is required, there must be a mechanism to report in a timely fashion. The reaction and investigation also needs to be reported to other facilities taking part in the collection or processing. The results of the investigation must also be reported to the Clinical Program reporting the reaction.

It is recognized that CBBs are challenged in evaluating causality of adverse reactions as they can only be in as much control as the information provided to them by a Clinical Program. At the very least, during the investigation, CBBs can verify their own work, such as donor screening and testing, cell counts, sterility cultures, equipment and reagent quality control, reagent acceptability, labeling, clerical transcription, SOP deviations, and accuracy of calculations. Clinical Programs meeting the FACT-JACIE Hematopoietic Cell Therapy Standards are required to notify CBBs of adverse reactions during administration and will be considered noncompliant if it is not provided.

Evidence:

The CBB must make available to the inspector SOPs describing how adverse reactions are investigated and reported, files of adverse reactions, and evidence that adverse reactions are reviewed and signed by the CBB Director or designee and reported to the appropriate agencies, if necessary.

Example(s):

Internal communication of adverse reaction investigations and conclusions may occur in various formats. Written reports should be prepared and signed by the appropriate individuals, including the CBB Director or designee. These written reports, and also tracking and trending, may be reviewed during a regularly scheduled QM meeting with inclusion in the meeting minutes. If applicable, results should be shared with other relevant staff.

CBBs listing their products in WMDA databases/registries must report serious adverse events to the Serious (Product) Events and Adverse Reactions (SPEAR) database, a WMDA-sponsored international centralized dataset of such events. SPEAR forms are located at <https://www.wmda.info>.

Different agencies have different required timeframes for reporting adverse events. The FDA requirements are to report significant adverse events (SAEs) within 15 days of their occurrence, whereas CIBMTR reports must be submitted within 30 days.

Regulatory agencies often have their own definitions of and reporting requirements for adverse events and serious adverse events, for example:

- EU: [European Union Tissue and Cells Directive \(EUTCD\)](#)
- U.S.:
 - Licensed unrelated CB units: [Guidance for Industry: Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products – Clarification of What to Report](#)
 - Unlicensed CB units: [21 CFR 1271.350\(a\)](#)
- Canada: [Guidance Document for Source Establishments - Reporting Adverse Reactions to Human Cells, Tissues and Organs](#)
- Australia: [Therapeutic Goods Administration](#)

STANDARD:

B2.12.7.2 Errors, accidents, biological product deviations, variances, and complaints shall be reported to other facilities performing CBB functions on the affected CB unit and to the appropriate regulatory and accrediting agencies, registries, grant agencies, and IRBs or Ethics Committees as necessary.

Explanation:

Each CBB should define errors, accidents, biological product deviations, and complaints, along with when and how each are reported. There must be a mechanism to report these events in a timely fashion to key individuals, including the CBB Director. The CBB is also expected to comply with institutional requirements and applicable governmental regulations pertaining to reporting. Besides regulatory and accrediting agencies, there may also be registries, grant agencies, or IRBs that require notification in selected situations. To the extent allowed by Applicable Laws, all such reports are for the purpose of quality assessment and improvement and shall be privileged and confidential.

STANDARD:

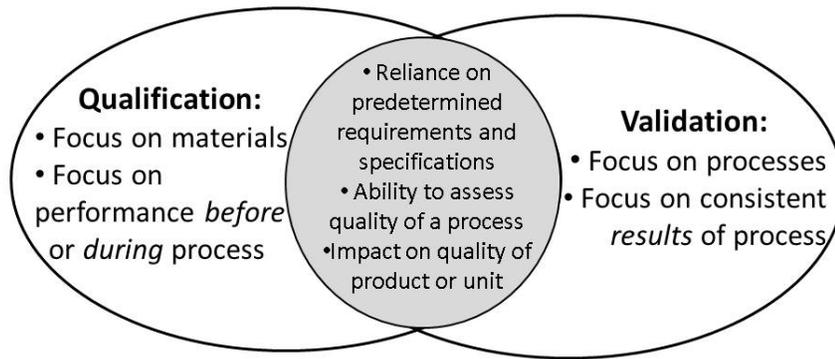
B2.13 The QM Plan shall summarize and reference policies and Standard Operating Procedures for qualification of critical vendors, equipment, supplies, reagents, and facilities.

B2.13.1 Qualification studies shall be reviewed and approved by the CBB Director and the Quality Unit.

Explanation:

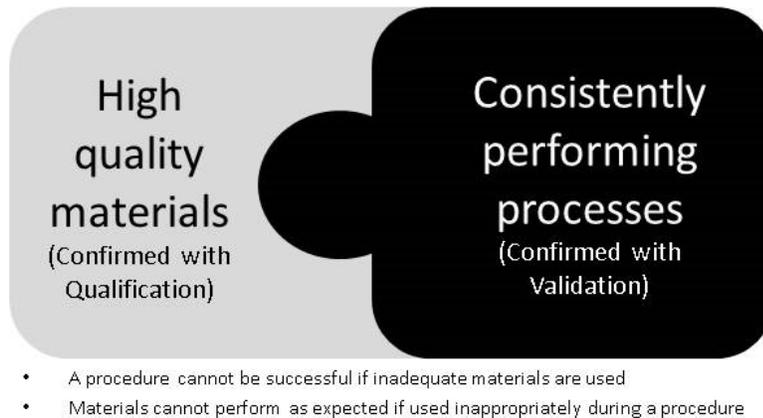
Qualification is defined as the establishment of confidence that equipment, supplies, and reagents function consistently within established limits. Sometimes qualification is confused with validation (required in B2.14), which is defined as confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. **Figure 2: Comparison and Contrast of Qualification and Validation** illustrates the differences and similarities between the two.

Figure 2: Comparison and Contrast of Qualification and Validation



While qualification and validation have two distinct objectives, they may be performed concurrently or sequentially. **Figure 3: Interdependency of Qualification and Validation** illustrates how the two processes work together.

Figure 3: Interdependency of Qualification and Validation



The timing of qualification and validation can enable CBBs to achieve synergies. When used in a sequential process, such as qualification before validation, it can help reduce duplicate efforts and streamline the assessment activities. When conducted concurrently, qualification and validation studies do not need separately-allocated resources. This is especially true for performance qualification, which is when materials are qualified for their intended use. When used concurrently, performance qualification is simply a subset of the validation procedure.

There will be situations when only one of the assessment activities is needed. For example, receipt of a new lot of a previously qualified reagent requires operational qualification to confirm sterility and functionality, but does not require a new validation study.

The QM Plan must include a process to qualify equipment, supplies, and reagents to confirm their consistent function in validated procedures. This process must include the establishment of minimum specifications for the acceptance of critical equipment, supplies, and reagents and must document that those specifications have been met before they are made available for use.

Equipment is qualified at installation (Installation Qualification (IQ)), often by the manufacturer at the time of purchase. Operational qualification (OQ) is performed by activities determining linearity, reproducibility, precision, and accuracy. Performance qualification (PQ) follows with calibration and quality control materials.

Evidence:

The CBB must provide the inspector the SOPs for qualification and validation. These should provide evidence of data collection, analysis, and evaluation, with follow-up of results. Specific qualification and validation studies must also be provided so that the inspector can verify the appropriateness of the study design, conformance to applicable SOP(s), and oversight from the responsible parties.

Example(s):

Consider qualification of a new centrifuge as an example. The centrifuge is installed in a CB Processing Facility and the manufacturer performs IQ at set-up, leaving documentation of this activity with the facility. The facility would then perform speed, timer, and temperature checks as a means to accomplish OQ. Finally, the facility would test products for expected nucleated cell recovery and viability to verify that the centrifuge is capable of meeting the expected endpoints of the processing procedure, and thus PQ.

An example of a sequential validation is when the CBB creates a new procedure related to collection. The first step could be to qualify all the intended materials before embarking on a validation study. This way, the CBB can be confident that it is using the appropriate materials and any negative results of the subsequent validation study would not be due to inadequate or inappropriate materials.

In the U.S., manufacture of licensed CB units requires reagent lot identity testing.

STANDARD:

B2.13.2 Qualification studies shall include verification that suppliers of critical supplies, reagents, services, and equipment comply with Applicable Law and these Standards.

Explanation:

All vendors providing equipment, supplies, and reagents must provide documentation indicating that their products are safe and perform to the standards required by the CBB, such as Certificates of Analysis or specification sheets. The CBB must have a system in place that verifies that vendors provide materials in a timely and consistent manner that meets the acceptance criteria defined by the CBB. Supplier qualification must also confirm that vendors are in compliance with Applicable Law and that there is a system in place that is consistent with these Standards (for example, evidence that the vendor can demonstrate process control). The CBB must evaluate and retain records of the specifications.

Example(s):

There are several ways to qualify a vendor of supplies, reagents, and services. The most effective is for the facility to perform an audit of the provider, but other more practical methods may include one or more of the following:

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

STANDARD:

B2.14 The QM Plan shall summarize and reference policies and Standard Operating Procedures for validation of critical procedures of the CBB.

Explanation:

Validation refers to confirmation by examination and provision of objective evidence that particular requirements are consistently fulfilled. Validation provides assurance that new or changed processes and procedures are capable of consistently meeting specified requirements. Process validation establishes that a process consistently produces a result or product [CB unit] that meets its predetermined specifications and performs effectively with regard to its intended use. Validation studies are required for all critical processes within the CBB, and must be repeated whenever there is a change in the process, including a change in equipment, reagents, or supplies.

Validation studies should be performed prospectively whenever possible. Prospective validations are those performed prior to the implementation of a new or revised process. However, concurrent validation (performed at the same time that a new or revised process is being performed, resulting in a product intended for use), or retrospective validation, based on accumulated production, testing, and control data may be acceptable in defined situations. Concurrent validation is useful for a relatively minor change, a change with a minimal probability of adverse outcome, and procedures that are rarely performed. Retrospective validation is useful for procedures that have been performed for a long time without substantive change.

Evidence:

SOPs for conducting validation and qualification, and example validation and qualification studies, must be available for inspector review. There should be a consistent mechanism 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. A sampling of validation studies of the facility, processes, and uses of equipment, supplies, and reagents should be provided. The design of the study should be adequate to determine if the new or revised process achieves the purpose for which it is intended. The validation studies must include documented review by the CBB Director and the Quality Unit. The inspector will note poorly designed or inadequately performed validation studies during the review process.

STANDARD:

B2.14.1 The Quality Unit and CBB Director or designee shall determine which procedures are considered critical.

Example(s):

Validation studies may be prioritized with the following criteria:

1. Focus on aspects for which failure to meet specifications could result in adverse event.
2. Conduct all specific studies required by the Standards.
3. Assess where the CBB is at particular risk for nonconformance.
4. Supplement with audits.

STANDARD:

B2.14.2 Each validation shall include:

B2.14.2.1 A validation plan, including conditions to be validated.

B2.14.2.2 Acceptance criteria.

B2.14.2.3 Data collection.

B2.14.2.4 Evaluation of data.

B2.14.2.5 Summary of results.

B2.14.2.6 Documentation of review and acceptance of the methodology by the Quality Unit.

B2.14.2.7 Review and approval by the CBB Director or designee of the validation plan, results, and conclusions.

Explanation:

B2.14.2 specifies the minimum requirements for each individual validation study. Validations should be performed at the aggregate level for several CB units (enough to provide reasonable assurances that the results could be applied to the entire inventory) rather than at the individual unit level. That is, the minimum number of samples used in validation studies will always be more than one. Statistical analysis is recommended when appropriate.

Validations must be designed to encompass key elements of the procedures, which are those parts of the process which impact cell viability and product integrity and quality. Validations begin with the design of a validation protocol. The validation protocol consists of a written plan stating how a validation will be conducted, including test parameters, product characteristics, production equipment, and decision points on what constitutes acceptable test results. Validations should include worst-case scenarios, a set of conditions encompassing upper and lower processing limits and circumstances, including those within SOPs, which pose the greatest chance of process or product failure when compared to ideal conditions.

STANDARD:

B2.14.3 Records shall be maintained to document that procedures have been validated to achieve the expected end-points, including viability of CB cells and CB unit characteristics.

B2.15 The QM Plan shall summarize and reference policies and Standard Operating Procedures for CB unit linkage that allow tracking from the infant donor to the recipient or final disposition and tracing from the recipient or final disposition to the infant donor.

B2.15.1 Linkage of the CB unit to the infant donor and mother shall be retained confidentially and indefinitely.

Explanation:

While linkage must be maintained, the identity should not be readily apparent in the later stages of processing and storage. With the requirement to maintain long-term linkage with the CB donor, there is information collected and stored that could allow tracing of the CB donor by an interested third party. The CBB must demonstrate processes in its record system that prevents the unnecessary display of such demographic information.

STANDARD:

B2.15.2 Documentation of all facilities involved in each stage of CB unit manufacturing shall be maintained.

B2.16 The QM Plan shall summarize and reference policies and Standard Operating Procedures to evaluate details of clinical outcome data and CB unit characteristics.

B2.16.1 The CBB shall obtain, maintain, and analyze sufficient critical outcome data to verify that the procedures in use in the CBB consistently provide a safe and effective product.

Explanation:

The CBB must maintain the outcome data outlined in E7 at a minimum. While it is understood that a CBB is not in control of a Clinical Program's responsiveness in providing outcome data, the CBB should make it clear in an agreement with the Clinical Program that it is required to obtain this information for analysis of quality, safety, and efficacy and demonstrate diligence in obtaining a high percentage of at least Day 100 and one-year outcome data.

Agreements with Clinical Programs should require the Clinical Program to furnish outcome data in so far as they concern the safety, purity, and potency of the CB unit involved. It is understood that obtaining the data depends on the Clinical Program; however, the CBB is expected to make reasonable attempts to obtain the data.

If the CBB relies on a third party to collect this data, there must be a system for timely sharing of information (especially with critical CB unit problems at time of receipt at the Clinical Program or at time of administration) in order for the CBB to meet quality control requirements.

It is especially challenging to receive complete outcome data in dual CB administration settings, especially where the CBB provides only one of the CB units. Outcome data is difficult for the CBB to interpret, because results can be skewed by possible interactions of the recipient and dynamics of engraftment of either of the units. It is important to document that the unit provided was part of a dual CB transplant and analyzed accordingly.

Example(s):

Outcome data provides valuable information necessary for evaluating the quality of a CB unit. For example, if an infusion reaction occurs, a CBB would want to use that data to investigate if their processes contributed to the event. A Clinical Program's thawing results compared to the CBB's own thawing results may shed light on the safety of the unit during transportation or shipping.

CBBs depend on Clinical Programs to provide outcome data. Possible methods to obtain the information include, but are not limited to:

- Obtaining the information directly from the CIBMTR or registry,
- Requesting that the Clinical Program enter into a written agreement to provide the data before releasing the CB unit,
- Performing routine requests to the Clinical Program to provide the data until received.

STANDARD:

B2.16.2 Both individual CB unit data and aggregate data shall be evaluated.

B2.16.3 Suboptimal results and complaints shall be investigated.

B2.16.4 Outcome data shall be trended to identify opportunities for improvement.

B2.17 The QM Plan shall summarize and reference policies and Standard Operating Procedures for the transfer of inventory that meet the requirements of B10.

Explanation:

Transfer of CB unit inventory has significant bearing on the quality of units and the information available to the accepting CBB. Even if no transfers of inventory are planned in the foreseeable future, CBBs must conduct planning to ensure any unexpected transfers protect the units and allow for the proper transition of records. At a minimum, policies or procedures must document how the bank plans to comply with the requirements in B10.

STANDARD:

B2.18 The Quality Unit Manager shall review and report quality management activities, at a minimum, quarterly.

Explanation:

The purpose of reporting on QM activities is to review the data and disseminate the information to the appropriate individuals. The CBB is responsible for identifying who should receive the reports.

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.

Evidence:

QM Program meeting records should provide evidence of reporting, as could signed reports, distributed communications, etc.

Quarterly reports can be based around minutes from the regular quality management meetings (if the frequency of the meetings is sufficient) and should summarize activities such as training performed, documents reviewed, audits performed, and procedures introduced or amended.

STANDARD:

B2.19 The Quality Unit Manager shall annually review the effectiveness of the QM Program. Documentation of the review findings shall be provided to the CBB Director.

Explanation:

An annual review of the overall effectiveness of the QM Plan must be performed by the Quality Unit Manager with findings provided to the CBB Director. The goal of this review is to verify the QM Program is detecting and correcting issues that impact the quality of CB units and improving the CBB's overall service.

The annual report must provide a year-long view of the overall function of the QM Plan, its effect on and interactions with the CB Collection Sites and CB Processing Facilities, and provide recommendations on areas for improvement. There should be documentation of measurement results, analysis, improvement activities, and follow-up measurement as indicated. The annual report should also contain trending information related to key indicators that are monitored, recipient outcomes, adverse events, or other important elements, utilizing data from at least the prior 12 months.

Example(s):

The CBB may wish to report on the performance of the QM Program more frequently than once a year. If so, there must be at least one review a year that utilizes data from the previous 12 months to provide a longitudinal perspective of how the QM Program is functioning over time.

B3: POLICIES AND STANDARD OPERATING PROCEDURES

STANDARD:

B3.1 The CBB shall establish and maintain policies or Standard Operating Procedures addressing critical aspects of operations and management in addition to those required in B2. These documents shall include all elements required by these Standards and shall address at a minimum:

Explanation:

These Standards require that each CBB has written policies and SOPs that address all important aspects of the CBB. The CBB 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 CBB or institutional standards vary from the minimal requirements, the CBB will be held to the higher standards.

The policies and SOPs may be generated within the CBB or in collaboration with other institutional infrastructures. This applies most often to SOPs addressing safety, infection control, biohazard disposal, radiation safety, and emergency response. In cases where general policies and SOPs are inadequate to meet the Standards or where there are issues that are specific to the CBB, the facility must develop its own policies and SOPs. In situations where institutional policies and procedures are utilized, there must be a defined mechanism within the CBB for initial review, review every two years, and approval of revisions.

CBBs should be aware that additional policies and procedures may be necessary to obtain the appropriate process approvals, train staff, facilitate consistency, and document compliance with the Standards. SOPs must comply with the NetCord-FACT Standards, and the table below should be used in conjunction with the Standards to verify that all required elements are included in the CBB's policies and procedures.

A list of required policies and procedures in the NetCord-FACT Standards is in **Figure 4: Required Policies and Standard Operating Procedures**.

Figure 4: Required Policies and Standard Operating Procedures

Subject	Standard
Written Agreements	B2.4, B10.2
Personnel Requirements and training	B2.5, B3.1.9, B5.1, D2.1.13
Change Control	B2.6
Document Control	B2.7, B2.7.2, B2.7.3, B2.7.4
Electronic Record Systems	B2.8, B3.1.29, B11.9.2, B11.9.4, B11.9.6
Interruption of Operations	B2.9, B12.1
Audits	B2.11
Errors, Accidents, Biological Product Deviations, Adverse Events, Variances, and Complaints	B2.12, C5.1.4
Qualification	B2.13, C3.1.19
Validation	B2.14
Tracking, Tracing, and Linkage	B2.15, C3.1.7, C3.1.8, C6.5
Outcome Data and Cord Blood (CB) Unit Characteristics	B2.16, B3.1.28, E7.1, E7.2
Donor Recruitment	B3.1.1, C3.1.1
Donor Management: maternal screening and testing	B3.1.2, B3.1.5, B5.5, C3.1.2, C3.1.4, C5.1.2, D2.1.1, D2.1.2, D2.1.7
Informed Consent	B3.1.3, C3.1.3
Donor Eligibility Criteria and Determination	B3.1.5, C5.1.2
Interaction Between the CB Collection Site and the CBB	B3.1.6, C3.1.5
Documentation of infant donor health at birth.	B3.1.7, C3.1.6

Subject	Standard
Collector training	C3.1.15
Collection of CB units, associated samples, and maternal samples	B3.1.10, B5.9.2, C3.1.8, C6.3
Completion of records at the CB Collection Site	B3.1.11, C3.1.9
Storage of CB units, associated samples, maternal samples, and documentation at the CB Collection Site	B3.1.12, C3.1.12, C6.7, D2.1.5
Transport and shipping of the CB unit, associated samples, maternal samples, and documentation to the CB Processing Facility	B3.1.13, C3.1.13, C7.4
Labeling of the CB unit, associated samples, reference samples, retention samples, maternal samples, and associated documents at the CB Collection Site at the CB Processing Facility and at release for administration	B3.1.14, B6.3.2.2, C3.1.10, C6.5, D2.1.4
CB unit acceptance criteria for receipt, processing, cryopreservation, and storage, including when risks have been identified	B3.1.15, B5.5.4, B10.3.4, D2.1.1, D2.1.8
Process control, including product specifications and nonconforming products	B3.1.16, D3.2.4, D5.1, D5.2, D6.3, D8.3.1, D8.3.2, D8.3.3
Storage of samples for testing	B3.1.17, D2.1.5
Acceptable levels of hemodilution of samples used for testing	B3.1.18, C3.1.14, D2.1.6
Communicable disease testing, microbial cultures, hemoglobinopathy testing, and other testing. Acceptance criteria for test results shall be described.	B3.1.18, B3.1.19, B3.1.20, D2.1.7, D9.1, D9.2, D9.4, D10.2
Notification of mothers or their responsible physicians, and governmental agencies when required, of positive or indeterminate communicable disease or genetic test results.	B3.1.20
Criteria for qualification and listing of CB units available for search and administration	B3.1.22
Listing, search, selection, reservation-of CB units	B3.1.23, E1.2, E1.2.1, E1.3, E1.6
Release and exceptional release of a CB unit	B3.1.24
For allogeneic use, verification that the infant donor and recipient are different individuals in the case of complete HLA matches	B3.1.26
CB unit recall, including a description of responsibilities and actions to be taken, including notification of appropriate regulatory agencies.	B3.1.27
Collection and analysis of transplant outcome data.	B3.1.28
Electronic record entry, verification, and revision.	B3.1.29, C3.1.16, D2.1.10
Data management	B3.1.30
CB unit records	B3.1.31, C3.1.17, D2.1.11

Subject	Standard
CB unit disposition	B3.1.32, C3.1.18, D2.1.12, D6.4, D8.1
Facility environmental management to include a description of environmental monitoring plan	B3.1.33, C3.1.20, D2.1.14
Materials management, maintenance and monitoring of equipment, qualification, cleaning and sanitation procedures to include identification of the individuals responsible for the activities, disposal of medical and biohazardous waste, hygiene and use of personal protective attire and equipment	B3.1.34, B3.1.35, B3.1.36, B3.1.37, B3.1.38, B7.5.3, C1.7, C3.1.19, C3.1.20, C3.1.21, C3.1.22, C3.1.23, C3.1.24, D2.1.15, D2.1.16, D2.1.17, D2.1.18, D2.1.19
Emergency and safety procedures	B3.1.39, C3.1.25, D2.1.20
Biological, chemical, and, if applicable, radiation safety	B3.1.40, B4.2, C3.1.26, D1.7.1, D1.7.3, D2.1.21
Disaster plan, including CBB-specific issues	B3.1.41, C3.1.27, D2.1.22
Confidentiality	B2.10, B5.8.2, B11.9.2
Inventory management	B2.17, B9.5, B10.1
Criteria for release from quarantine including nonconforming	B3.1.21
HLA Typing	B3.1.25, D2.1.9
CB unit disposal	B3.1.42, C3.1.28, D2.1.23
Review of records and transportation and shipping record requirements	E2.1, E6.4

Evidence:

Unless specified otherwise, the Standards do not prescribe whether a topic must be in a policy, procedure, or both so long as the idea is addressed in writing in one of these quality documents. Furthermore, a dedicated policy or procedure is not required for each of these ideas; one or more of the required topics may be included in a single document.

In cases where multiple topics are covered by a single SOP, it will aid the inspection process if the CBB prepares a crosswalk between the list of required procedures, and the CBB's own SOP Manual.

The inspector should verify that policies and procedures are followed and that they are comprehensive and define all aspects of the CBB 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 SOP Manual with the pre-inspection material prior to the on-site inspection. The Table of Contents should be examined for evidence of the existence of SOPs addressing each item listed in the Standards before arriving at the inspection site. Prior confirmation that a specific SOP has been generated will reserve limited on-site inspection time for evidence of implementation of written procedures and other activities that can only be verified in person at the inspection site.

STANDARD:

B3.1.1 Donor recruitment and education.

Explanation:

Donor recruitment policies must describe how a CBB informs potential participants or customers of their service and potential participation. SOPs must also delineate donor acceptance criteria. This standard does not imply that marketing strategies are revealed in policies and SOPs, but that recruitment policies adequately instruct personnel to properly perform these duties.

STANDARD:

B3.1.2 Maternal screening and testing (including interpretation and acceptable results).

Example(s):

A uniform donor questionnaire is on the FACT website at www.factwebsite.org > Education and Resources > Resources.

STANDARD:

B3.1.3 Informed consent.

B3.1.4 Suitability assessment of maternal and infant donor.

B3.1.5 Donor eligibility criteria and determination.

B3.1.6 Interaction between the CB Collection Site and the CBB.

B3.1.7 Documentation of infant donor health at birth.

B3.1.8 Maintenance of linkage of the CB unit to the infant donor and mother.

B3.1.9 Personnel training and continued competency for the procedures performed.

B3.1.10 Collection of CB units, associated samples, and maternal samples.

B3.1.11 Completion of records at the CB Collection Site.

B3.1.12 Storage of CB units, associated samples, maternal samples, and documentation at the CB Collection Site.

Explanation:

Validation data should prove that the storage conditions do not affect the quality of the CB unit. If storage of units or samples is to be at room temperature at any time, the acceptable temperature range of room temperature must be defined.

Example(s):

In the U.S., the FDA indicates liquid CB units are to be stored at 15-25°C.

STANDARD:

- B3.1.13 Transport and/or shipping of the CB unit, associated samples, maternal samples, and completed records to the CB Processing Facility.*
- B3.1.14 Labeling of the CB unit, samples, and records at the CB Collection Site, at the CB Processing Facility, and at release for administration.*
- B3.1.15 Acceptance criteria for CB unit receipt, processing, cryopreservation, and storage.*
- B3.1.16 Process control, including product specifications and management of nonconforming products and processes.*
- B3.1.17 Storage information including sample location and storage temperature of associated, representative, reference, retention, and maternal samples for testing.*
- B3.1.18 Acceptable levels of hemodilution of maternal samples used for communicable disease testing.*
- B3.1.19 Communicable disease testing, microbial cultures, hemoglobinopathy testing, and other testing. Acceptance criteria for test results shall be defined.*
- B3.1.20 Notification of mothers or their responsible physicians and governmental agencies of positive or indeterminate communicable disease or genetic test results.*

Explanation:

The rationale for reporting indeterminate or unconfirmed reactive screening results is to alert physicians and mothers of potential health-related issues. It is the CBB's responsibility to define who actually contacts the mother. Because communication of genetic testing results can be sensitive, only qualified people should provide the results to the infant donor's mother.

Maternal samples must be drawn within seven days before or after delivery to reflect the mother's infectious status at the time of CB unit collection. Retesting donors after six months after delivery is not practical in many CB banking settings. Therefore, interpretation of indeterminate or repeatedly reactive test results often cannot be concluded by the CBB. Since the risk of transmission remains, abnormal results must be communicated to the mother or her physician so that appropriate follow-up can occur.

Example(s):

There may be regulations that require the CBB to report certain results to governmental agencies, such as the state department of health.

STANDARD:

- B3.1.21 Criteria for release of CB units from quarantine, including nonconforming CB units.*
- B3.1.22 Criteria for qualification and listing of CB units for search and administration.*

Explanation:

Individual CBBs must develop criteria including at a minimum the specifications listed in Appendix V, Specification Requirements, ensuring accuracy/relevance of testing methods and recovery of viable progenitor cells, and follow them accordingly.

Example(s):

Examples of other qualification parameters designed in the U.S. include, for example, those developed by the NMDP Quality Standards Committee and the Health Resources and Services Administration (HRSA) solicitation, which were designed with input from transplant physicians to reflect nationally accepted standards and for financial viability. Table A in the FDA guidance, "Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications," also includes qualification parameters for licensure. While these parameters were developed for use in the U.S. and for CB units imported to the U.S., they may be applicable in other countries as well.

STANDARD:

B3.1.23 Listing, search, selection, and reservation of CB units.

B3.1.24 Release and exceptional release of a CB unit.

B3.1.25 HLA typing to include requirements for resolution, loci, timing, and verification.

Explanation:

Two tests are required for HLA typing, one performed at the time of banking and one performed on a sample from an attached segment after the CB unit has been frozen and stored. All verification typing of units must be reviewed and verified against the original typing as a means to confirm unit identity. Discrepancies must be resolved before a unit can be released.

Example(s):

The verification HLA typing may be performed by a laboratory other than that used by the CBB for initial typing, such as the potential Clinical Program or a central laboratory designated by a registry.

STANDARD:

B3.1.26 For allogeneic use, verification that the infant donor and recipient are different individuals in the case of complete HLA matches.

Explanation:

This standard is in place to prevent the use of an autologous unit when the intended purpose is an allogeneic transplant. Donor families may forget that they donated CB and the Clinical Program is blinded from the identity of the donor.

Example(s):

One approach to ensuring that a donor and recipient are not the same individual is for the Clinical Program to verify that donor and recipient date of birth are not the same or supply adequate information to the CBB, such as recipient date of birth, so that the verification can take place at the bank.

STANDARD:

- B3.1.27 CB unit recall, including a description of actions to be taken, responsible personnel, and notification of appropriate regulatory agencies.*

Explanation:

The procedure for CB unit recall will include elements of unit return and reissue, but must additionally address situations in which the CBB must recall a distributed unit. CBBs distribute units to multiple Clinical Programs in advance of the day of administration, making recall a possible event.

Example(s):

CBBs with a BLA with the U.S. FDA must follow 21 CFR 211.150, which requires that the distribution of a CB unit can be readily determined to facilitate recall.

STANDARD:

- B3.1.28 Collection and analysis of transplant outcome data.*
- B3.1.29 Electronic record entry, verification, and revision.*
- B3.1.30 Data management.*
- B3.1.31 CB unit records.*
- B3.1.32 CB unit disposition.*

Example(s):

Disposition is defined as the current status, location, or use of a CB unit. The disposition of a unit could, for example, be stored, discarded, released for administration, administered, designated for research, etc.

STANDARD:

- B3.1.33 Facility management, including a description of environmental monitoring.*
- B3.1.34 Materials management.*
- B3.1.35 Equipment monitoring, qualification, and maintenance.*
- B3.1.36 Cleaning and sanitation procedures.*
- B3.1.37 Disposal of medical and biohazardous waste.*
- B3.1.38 Hygiene and use of personal protective attire and equipment.*
- B3.1.39 Emergency and safety procedures.*

Explanation:

SOPs addressing safety, infection control, biohazard waste disposal, and radiation safety.

STANDARD:

B3.1.40 Biological, chemical, and, if applicable, radiation safety.

B3.1.41 A disaster plan to provide for continuous safe storage and transport and shipping, if applicable, of the CB units.

Explanation:

A method to describe how a CBB deals with the scope of possible events that constitute real threats to the personnel and inventory must be prescribed. It should identify internal disasters (such as loss of vacuum in a liquid nitrogen tank) and external disasters (such as loss of power in a building structure in severe weather or other natural event). These disaster plans will vary based on regional issues but must address how the CBB will continue its core operations in the event of a disaster.

Example(s):

Many facility management policies and SOPs are maintained at the institutional level, which is acceptable. However, the CBB must address CB banking-specific issues. This may include specific procedures for maintenance and monitoring of equipment not used elsewhere or not covered in the institution's overall procedures, or specific procedures for how to handle a CB unit in the middle of processing in the event of a disaster.

The disaster plan may distinguish steps to take for minimal disasters in addition to major disasters. They may also include a business contingency plan.

STANDARD:

B3.1.42 Disposal of CB units.

B3.2 The CBB shall maintain a detailed Standard Operating Procedures Manual that includes at a minimum:

B3.2.1 A table of contents.

B3.2.2 A standardized format for policies, procedures, worksheets, forms, and labels.

Explanation:

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

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

Typically, the SOP Manual is maintained separately from the actual QM Plan, but it must still comply with the QM Plan's requirements, such as document control. A written copy or electronic version (with provision of hardcopy as necessary) of the CBB's policies and SOP Manual (including Work Instructions at CBBs following

ISO 9000) must be immediately available to all relevant employees in their working environments. Any copies of the policies and SOP Manual must be identical to the source document and those copies must not be used to alter, modify, extend, delete, or otherwise edit any SOP. Only current SOPs shall be available to the staff performing the work. SOPs that have been retired shall be accessible for reference as needed for audits or other quality control purposes.

Evidence:

The written copy or electronic version of the SOPs should be organized in such a manner for the inspector to ascertain that the SOPs and policies are comprehensive, defining all aspects of the CBB.

STANDARD:

B3.2.3 Documented approval and date of approval of each Standard Operating Procedure by the CBB Director, Quality Unit Manager, and relevant personnel prior to implementation, upon procedural modification, and at least every two (2) years after implementation.

Explanation:

Although the Standards indicate that an individual designated by the CBB Director may review procedures every two years, the CBB Director remains ultimately responsible for this process. The designated individual must be knowledgeable, by virtue of education or training, of the subject matter being discussed in the SOPs.

The review of SOPs, policies, and worksheets every two years is intended to confirm that the documents accurately reflect current practices. Whenever a change in practice is introduced, the relevant controlled documents must be implemented or revised before the change is put into effect.

In CBBs where an electronic document control system is implemented, signatures may be electronic. However, when the SOPs are sent in paper format to sites where access to the electronic system is not available (e.g., CB Collection Sites), they should be physically signed.

Evidence:

A review of the SOP Manual should demonstrate that, in addition to the review every two years, revisions are made throughout the year in conjunction with changes in practices.

STANDARD:

B3.3 Standard Operating Procedures shall be sufficiently detailed and unambiguous to allow qualified staff to follow and complete the procedures successfully. Each individual Standard Operating Procedure shall include:

Explanation:

The "SOP for SOPs" provides a standardized format for master documents (policies, SOPs, orders, worksheets, forms, reports, agreements, letters, and labels). The "SOP for SOPs" should be clear and easy to use. It should also be available for personnel to use as a template and should assist personnel with placing information in the correct headings of documents. A checklist to use during SOP creation or revision can be very useful to assure that all elements are included and correct before implementation.

The “SOP for SOPs” also outlines the method by which the CBB creates, amends, reviews, approves, distributes, implements, updates, and archives master documents in order to ensure that all staff uses the latest authorized versions. These factors are crucial to define should the need arise to review what policies and procedures are in place currently and also what were in place at any given time in the past.

Standardization of SOPs should include a system for numbering and titling that allows for unambiguous identification of procedures. The CBB should be consistent in the design of reports, worksheets, and forms. The policies and SOPs must be detailed, be unambiguous, and adequately define all operational aspects of the CBB.

Evidence:

All elements of an SOP must be present as defined in the “SOP for SOPs” and there must be consistency in format from one SOP to another.

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

STANDARD:

B3.3.1 A clearly written description of the objectives.

B3.3.2 The personnel responsible for its execution.

B3.3.3 A description of the facility, equipment, and supplies.

Explanation:

This description provides a “shopping list” of items that are required to complete a procedure.

STANDARD:

B3.3.4 A stepwise description of the procedure.

Example(s):

Though not required, the inclusion of diagrams and tables within policies and SOPs may be helpful to facilitate understanding of the procedure. Process flow charts can be also used to illustrate procedures effectively.

STANDARD:

B3.3.5 Acceptable end-points and the expected range of results, if applicable.

Explanation:

End-points and range of expected results, where applicable, provide safety checks in procedures before progressing to the next step.

STANDARD:

B3.3.6 Reference to other Standard Operating Procedures or policies required to perform the procedure.

Explanation:

Reference to other SOPs or policies provides additional information to completely carry out a process and reduces length of the SOPs through elimination of redundant language.

STANDARD:

B3.3.7 A reference section listing appropriate literature, if applicable.

Explanation:

References provide direction to documents or other resources that can provide additional information on the content of the SOP.

STANDARD:

B3.3.8 Reference to the current version of worksheets, forms, reports, and labels, where applicable.

Explanation:

Worksheets, forms, reports, and labels, must be referenced in appropriate SOPs. The purpose is to be assured 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.

Example(s):

They may be included in various ways. For example, they may be included within the SOP itself or referenced in the SOP as a separately controlled document. However this is done, they must be under document control.

STANDARD:

B3.4 All policies and Standard Operating Procedures shall comply with these Standards.

Evidence:

The CBB is responsible for verifying that CB Collection Sites' SOPs are appropriate for the collection of CB. For banks that have many sites where infrequent collections occur, the bank should show evidence that it provides appropriate training materials, instructions, collection materials, and SOPs to the collectors.

STANDARD:

B3.5 All personnel at the CBB, CB Collection Sites, and CB Processing Facilities shall follow the applicable policies and Standard Operating Procedures established by the CBB.

Explanation:

The written copy or electronic version (with provisions for hard copies as necessary) of the CBB's policies and procedures relevant to the work schedule and duties must be immediately available to all relevant employees in their working environment. Similar to the ability to divide related procedures into different

SOP Manuals, programs may choose to only have necessary procedures to perform specified processes at a workstation. However, all procedures that an employee must comply with must be readily available to him/her for reference when needed.

CBBs relying entirely on an electronic document management system should have hard copies for critical safety and emergency procedure SOPs in case of complete failure of the electronic systems.

Evidence:

The written copy or electronic version of the SOPs should be readily identifiable to the inspector. The inspector should expect to see the SOP manual or electronic access to SOPs in all performance areas of the CBB. The SOPs should be organized in such a manner for the inspector to ascertain that the SOPs are comprehensive, defining all aspects of the Clinical Program.

STANDARD:

B3.6 Review by and/or training of a staff member shall be documented before the staff member is allowed to perform new and revised Standard Operating Procedures.

Explanation:

Before a staff member is allowed to perform a new or revised procedure, he/she must have reviewed the new procedure and received appropriate training. CBBs are not required to train all staff members before implementing a new policy or procedure, but must document an individual's review and training before that person uses the revised policy or procedure.

Evidence:

It is expected that a correlation between process and SOPs can be observed. Personnel shall demonstrate an understanding that they are required to follow relevant SOPs.

Example(s):

A new or revised SOP could be implemented while a member of the staff is on maternity or paternity leave, but that staff member must read the SOP and, if applicable, be trained upon her/his return before performing the procedure.

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

STANDARD:

B3.7 Current versions of policies and Standard Operating Procedures relevant to the processes being performed shall be readily available to personnel.

Evidence:

Procedures available at the time of inspection must be the ones currently in use, whether available electronically or in conventional paper format. This must be proven by a system of versioning and distribution control.

Example(s):

If document tracking and management is not provided by the central CBB, there should be document tracking and management in place at the CB Collection Sites.

To provide non-fixed CB Collection Sites access to the policies and SOPs, a CBB may provide them in paper format or on a flash drive included in the collection kit.

Electronic access to policies and SOPs is acceptable; however, there must be a back-up plan for access to these documents when the electronic system fails. Back-up plans may be DVDs containing copies of the documents, power back-ups, or paper copies.

B4: FACILITIES AND SAFETY

STANDARD:

- B4.1 All facilities, including administrative space, shall be safe and secure.*
- B4.1.1 The space shall be of adequate size, construction, and location to maintain safe operations, prevent contamination, and promote orderly handling.*
 - B4.1.2 The space shall be secure to prevent the admittance of unauthorized individuals.*
- B4.2 There shall be policies and Standard Operating Procedures for biological and chemical safety as appropriate, including:*
- B4.2.1 Communicable disease agents.*
 - B4.2.2 Hand washing.*
 - B4.2.3 Chemical hygiene.*
 - B4.2.4 Fire safety.*
 - B4.2.5 Power failures.*

Explanation:

Policies and SOPs 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 must have appropriate personal protective equipment available to them. The type of exposure that may be encountered will determine the appropriate protection. If aerosol exposure is likely, masks, goggles, and gowns or aprons should be provided. Gloves must be provided whenever potential exposure exists. There must be written instructions for action to be taken in case of exposure to communicable disease agents.

Evidence:

During the inspection, the inspector will observe personnel for use of protective clothing and other biosafety precautions. Employees' personnel files must document training in safety procedures. The presence of unused equipment, excessive traffic from unauthorized personnel, and inappropriate storage of reagents and supplies may indicate an unsafe environment.

Example(s):

Specific safety procedures may be maintained within a designated Safety Manual or may be incorporated into the relevant SOPs. Safety training, including universal precautions ("standard" precautions per the U.S. Centers for Disease Control) for handling blood is a requirement of the Occupational Safety and Health Administration in the U.S.; and equivalent regulations apply in other countries.

B5: CORD BLOOD BANK OPERATIONS

STANDARD:

B5.1 A CBB that includes multiple CB Collection Sites or CB Processing Facilities shall employ coordinated policies and Standard Operating Procedures, protocols, staff training and competency evaluation procedures, and quality management systems.

B5.2 A CBB that includes multiple CB Collection Sites or CB Processing Facilities shall demonstrate evidence of regular interaction between the CBB and these sites or facilities.

Explanation:

There are many organizational approaches used by Cord Blood Banks (CBB) with varying centralization of process control by the CBB. The bank must describe whether the CB Collection Site(s), CB Processing Facility or Facilities, and registry are separate entities; whether CB collections are performed at fixed or non-fixed collection sites or a combination of both; whether collections are performed by dedicated collection personnel, obstetric personnel, or both; and whether collections are performed *in utero*, *ex utero*, or both. The approach to training, competency assessment, performance evaluation, and the management of distribution of supplies, CB units, and records.

Agreements with CB Collection Sites define the extent of their responsibility, are signed by authorized parties from the CBB and the Collection Site, and are reviewed periodically and updated.

The CBB must either manage the scope of activities related to the collection of CB at the CB Collection Site or have a very close working relationship with the CB Collection Site. The CBB should be able to demonstrate interactions between the CBB and CB Collection Sites that are commensurate with the degree of autonomy of the sites.

The CB unit is the end-product of a series of processes: collection, screening, testing, processing, and storage. It is not possible to evaluate a CB unit in isolation of the screening and collection. In the unrelated donor setting, there are more stringent requirements in the initial donor screening and collection procedures. This may be the only opportunity to elicit family infectious disease risk and genetic screening information given limited follow-up ability post collection. Additionally, the privacy and donor safety requirements are essential to protecting the rights and wellbeing of the infant and maternal donor. The CBB must ensure that the collection procedures are compliant with these Standards and that the collection process is monitored by its QM program.

Example(s):

Application of this standard to collections performed in non-fixed CB Collection Sites may be challenging. A CBB using a non-fixed site usually has a standard collection practice that is communicated to the collection staff. Various methods of communication can be effective, including letters directly to licensed health care providers when they assume responsibility for collecting a CB unit, and instruction sheets in each collection kit directed to the collector. Generally there is ongoing interaction between the collection staff and the CBB staff, who provide support from the time of enrollment through the transport or shipping of the unit to the CB Processing Facility. For related collections at non-fixed sites, the business relationship is usually between the family and the CBB, not directly between the CB Collection Site and CBB; therefore, documentation of training and competency at the CB Collection Site may be challenging.

STANDARD:

B5.3 Records of each CB unit shall be made concurrently with each stage of donor management and CB unit collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, and distribution or disposal in such a way that all steps may be accurately traced.

B5.3.1 Records shall identify the person immediately responsible for each step from the donor to the recipient or final disposition of the CB unit and from the recipient or final disposition to the donor, including appropriate dates and times to provide a complete history of the work performed and to relate the records to a particular CB unit.

Explanation:

CBBs must be able to track and trace the CB unit from donor management and collection to final disposition and vice versa. CBBs may not have immediate access to information regarding administration of the unit, but should attempt to obtain this information from the Clinical Program. It is recognized that the CBB may be limited by what information Clinical Program provides; however, the CBB must make a reasonable attempt to obtain the information. These efforts must be documented.

Evidence:

The CBB must be able to produce records that demonstrate the ability to accurately track and trace the CB unit through donor management, collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, and distribution or disposal.

STANDARD:

B5.3.2 Records shall be as detailed as necessary for a clear understanding by a person experienced in CBB procedures.

B5.4 The CBB shall have an established relationship with each fixed CB Collection Site to facilitate implementation of and compliance with the CBB QM Program and Standard Operating Procedures.

Explanation:

For collections at fixed sites, there must be a written agreement between the CB Collection Site and the CBB.

STANDARD:

B5.5 There shall be maternal and infant donor evaluation procedures in place to evaluate the risk of infectious and genetic disease transmission from CB units.

B5.5.1 Maternal and infant donor evaluation shall be reviewed by trained CBB personnel.

B5.5.2 Maternal and infant donor eligibility shall be determined based upon results of screening and testing in accordance with Applicable Law.

B5.5.3 Risks of genetic or malignant disease transmission from the CB unit shall be determined based upon results of donor screening and testing.

B5.5.4 The CBB shall have policies regarding the acceptance of CB units if there is a risk of communicable, genetic, or malignant disease transmission.

B5.5.4.1 The CBB Medical Director shall give specific authorization to accept CB units if the genetic or medical history of a first-degree relative of the infant donor is unknown, in accordance with Applicable Law.

Explanation:

These donor evaluation criteria must meet all applicable local and national laws. International laws may also apply. The CBB is not expected to perform genetic testing, but to obtain the history of genetic testing of the infant and maternal donors from the donor family. The genetic testing performed on infant and maternal donors will likely be based on the population of the geographic region, Applicable Law, or family history.

CBBs may have different screening criteria for genetic diseases among different populations. However, the criteria for determining eligibility in terms of communicable diseases should be the same, although banks may manage the CB units differently (for example, between unrelated and related CB units).

Example(s):

The HTA "Guidance document for establishments working with umbilical cord blood" (November 2010) states that the CBB should have a policy on what steps would be taken if a CB unit stored for autologous use and meeting only requirements for autologous testing was requested to be released on an allogeneic basis. This document can be found at

http://www.hta.gov.uk/db/documents/Cord_Blood_Guidance_Document.pdf.

CBBs that import CB units into the U.S. are subject to U.S. regulations. More information for the U.S. can be found in the FDA's Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) at <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM091345.pdf>

FDA published the guidance, "Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products," to provide recommendations for screening donors of HCT/Ps for risk of transmitting the Zika virus. FDA now considers the virus a relevant communicable disease or disease agent (RCDAD) as defined in 21 CFR 1271.3(r)(2). Therefore, review of relevant medical records must indicate that a potential donor of HCT/Ps is free from risk factors for, or clinical evidence of, Zika virus infection for the purpose of determining donor eligibility. Newer guidance may be issued, and other countries may have additional guidelines. This document can be found at: <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM488582.pdf>

STANDARD:

B5.5.4.2 The CBB shall have policies to assess deferral of a donor or collected CB unit from unrelated use if there is a family history of a genetic or malignant disease that could be transmitted to a recipient unless testing or follow-up excludes the risks.

Explanation:

The CBB policies and SOPs must require that CB units are evaluated for the potential of inherited disorders or history of disease that may be transmissible, and must also specify when CB units deemed positive for these risks should not be kept in inventory in the unrelated allogeneic setting if testing or follow-up do not exclude the risks. CBBs may be in a jurisdiction in which Applicable Law defines when a unit must be deferred.

The CBB must determine acceptability of genetic conditions based upon available testing or possibility of follow-up for reasonable assurance the CB unit will not transmit genetic diseases. The unit shall not be accepted if there is not acceptable follow-up or testing. CBBs must document their evaluation process in SOPs.

Example(s):

CBBs may defer all CB units with a risk of transmitting genetic diseases or have a decision tree with certain criteria for acceptance or deferral.

STANDARD:

B5.5.5 When a mother does not meet the established screening criteria, the CBB Medical Director and the Quality Unit shall document and maintain in the permanent record the nature of the nonconformance and the rationale for inclusion of that CB unit.

Explanation:

This standard applies to CBB acceptance criteria and donor eligibility. Donor eligibility criteria will vary depending on Applicable Law.

Screening criteria should be available to trained personnel performing the medical history screening and CBB personnel. Although maternal screening is required of all CBBs, related CBBs may choose to store nonconforming CB units. CBBs must have a policy for such criteria and this must be available to those obtaining the medical history and CBB personnel.

STANDARD:

B5.6 The CBB shall use HLA testing laboratories that are capable of carrying out DNA-based intermediate and high resolution HLA-typing and are appropriately accredited by the American Society for Histocompatibility and Immunogenetics (ASHI), European Federation for Immunogenetics (EFI), or other accrediting organizations providing histocompatibility services appropriate for cord blood banking.

Explanation:

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

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

In addition to ASHI and EFI, other HLA typing laboratory accrediting organizations may be deemed appropriate based on standards that adequately address cord blood banking and on accreditation processes that use qualified inspectors and a consistent review procedure. The FACT Guidelines for Histocompatibility Typing Standards and Accreditation Programs will be used to evaluate accrediting organizations that wish to be considered appropriate for cord blood banking. It is incumbent on those other accrediting organizations to provide demonstrable evidence that they meet the guidelines. If a bank wishes to use a HLA typing laboratory with accreditation other than ASHI or EFI, that bank must ensure the alternative accreditation has been determined to be acceptable. CBBs requesting accreditation using a HLA typing laboratory not accredited by ASHI or EFI must notify FACT as soon as possible.

Evidence:

A copy of the current (in-date) ASHI or EFI certificate for the laboratory is required. If ASHI accreditation is not for HSC/BM Transplantation, the CBB must describe the role the HLA testing laboratory fulfills in donor selection and the HLA expertise in the program.

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

STANDARD:

B5.7 All laboratories utilized by the CBB for testing of reference samples and maternal samples shall be accredited, certified, or licensed to perform such testing in accordance with Applicable Law.

B5.7.1 The CBB shall maintain documentation of the accreditation, certification, or licensure of these laboratories to perform this testing.

- B5.7.2 *When external laboratories are used for any aspect of reference sample or maternal sample testing, the CBB shall maintain a record of all samples sent to such laboratories, including the identifiers, results, date sent, and date results are received.*

Explanation:

CBBs shall maintain current accreditation, certification, or licensing documentation of the laboratories selected to perform testing and retain information regarding the name and version of the assays used in testing. This information does not need to appear on the label, but should be available if needed.

Evidence:

CBBs should be able to produce copies of current accreditation certification or licensing documentation of external laboratories selected to perform testing and the name and version of the assays used in testing.

CBBs must produce records relating to samples sent to external laboratories that include the identifiers, results, date sent, and date results were received.

STANDARD:

B5.8 *Confidentiality.*

- B5.8.1 *There shall be a process for maintenance of confidentiality of all records and communications among the CBB, the CB Collection Sites, the CB Processing Facility, testing laboratories, registries, and Clinical Programs according to Applicable Law.*

- B5.8.2 *The CBB shall have written policies and Standard Operating Procedures for circumstances where the infant donor's mother or legal guardian and/or her physician could be contacted.*

Explanation:

The CBB should request that the Clinical Program not reveal confidential information to the recipient, the recipient's family, or clinical personnel. While transplant coordinators and laboratories require details to select donors and confirm product identity, Clinical Programs should respect the confidentiality of donors and limit the communication of information that could potentially identify the donor. Recipient families will naturally be curious about the donor and the source providing the CB unit, and, for example, the combination of CBB and date of birth could provide the recipient with information adequate to trace the donor. It is the role of the CBB and the listing registry to educate Clinical Programs about potential breaches of confidentiality.

STANDARD:

B5.9 *There shall be Standard Operating Procedures to monitor the continuing adequacy of the procedures, equipment, supplies, and reagents as used under routine operating conditions by the CBB personnel.*

- B5.9.1 *The results of ongoing internal monitoring shall be documented and checked, and trends shall be analyzed on a regular basis.*

- B5.9.2 *If cord tissue is collected for testing, procedures for tissue collection, processing, and storage shall be fully integrated into the QM Plan.*

Explanation:

Monitoring is similar to auditing but represents a more regular check of the same routine indicators. Both audits and monitors are conducted to assure that the QM Program is operating effectively and to identify trends and recurring problems. Both are designed to result in improved processes and outcomes. Both can focus on broad processes or very specific components of a process.

Results of monitors and audits can indicate the need for further corrective or preventive action or both. The frequency for data collection and analysis of monitoring should be established in accordance with the QM Plan. Some indicators may be reported concurrently with each occurrence while others may be retrospectively analyzed and reported at defined intervals. Once collected, the data should be analyzed and assessed for improvement opportunities. Strategies for 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.

Evidence:

There should be documentation of results, analysis, improvement activities, and follow-up assessment as indicated.

Example(s):

Examples of elements to be monitored include cell recovery, viability, and bacterial contamination. A CBB might monitor the number of CB units that do not meet minimum volume criteria to assess a collector's performance. A CB Processing Facility may track its average nucleated cell recovery and viability from month to month to demonstrate that the process is in control or to detect a trend. In the same way, a CB Processing Facility could track its bacterial contamination rates which could lead to an investigation of collection techniques, processing method, or environmental conditions.

STANDARD:

B5.10 Institutional Review Board or Ethics Committee Requirements.

B5.10.1 In compliance with Applicable Law, the CBB shall have formal review of investigational protocols and maternal consent for CB banking and related activities by a mechanism that is approved by the appropriate governmental authority.

B5.10.2 The CBB shall maintain documentation of all its research protocols, Institutional Review Board or Ethics Committee approvals or equivalent, correspondence with regulatory agencies, investigational new drug or device exemptions, annual reports, and any adverse events.

Evidence:

Inspectors should be aware of variable IRB practices among institutions. Some IRBs do review routine unrelated donation of cord blood, while others consider that routine CB collection and banking does not constitute human subject research, and therefore these procedures do not require IRB review.

Example(s):

In the U.S., the appropriate governmental authorities include the Office of Human Research Protections under the Department of Health and Human Services (HHS) and the FDA. Minimally manipulated CB units that are intended for related use only are regulated solely under the authority of section 361 of the PHS Act (21 CFR 1271) and are not subject to IRB/IND or licensing requirements. CBBs with minimally manipulated, unrelated allogeneic CB units may be subject to IRB, IND, or BLA requirements.

The following are examples of appropriate governmental authorities in other geographical regions:

- United Kingdom (UK): Human Tissue Authority
- Australia: Therapeutic Goods Administration, and
- Canada: Health Canada.

B6: CODING AND LABELING OF CORD BLOOD UNITS

STANDARD:

B6.1 ISBT 128 Coding and Labeling.

B6.1.1 CB units shall be identified according to the proper name of the product, including appropriate attributes, as defined in ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions.

Explanation:

ISBT 128 is the international information standard for transfusion and transplantation. The use of ISBT 128 for all cellular therapy products provides a uniform coding and labeling system worldwide. ISBT 128 is an international standard for the transfer of information associated with human tissue transplantation, cellular therapy, and blood transfusion. It provides for a globally unique donation numbering system, internationally standardized product definitions, and standard data structures for bar coding and electronic data interchange. Initially, ISBT 128 was developed for blood and blood component transfusion to increase the capacity for electronic data, to increase the security and accuracy, and to permit unique unit identification globally. ISBT 128 now includes cellular therapy products and tissues. ICCBBA is the not-for-profit organization (www.iccbba.org) that is responsible for the development and maintenance of the ISBT 128 standard. ICCBBA maintains the databases for facility identification and product coding, assigns new product codes, and provides technical support.

Several volunteer technical advisory groups support and inform ICCBBA. The Cellular Therapy Coding and Labeling Advisory Group (CTCLAG) includes international representation from FACT, JACIE, ISCT, ASBMT, EBMT, NMDP, WMDA, and AABB. CTCLAG was formed to recommend standard definitions for cellular therapy products and rules for future assignment of cellular therapy product codes, to draft labels and a labeling strategy for cellular therapy products, and to draft an implementation plan. The work of CTCLAG can be found in the following publications:

- Ashford, P. et al: *Standards for the Terminology and Labeling of Cellular Therapy Products*. Transfusion 2007; 47:1319-27

- Ashford, P. et al: *ISBT 128 Implementation Plan for Cellular Therapy Products*. Transfusion 2007; 47:1312-8

The two main pieces of the standard terminology to unambiguously describe a product are class and attributes. Classes are broad descriptions of products (such as HPC, Cord Blood) and attributes are additional characteristics that uniquely define the product. There are also optional characteristics that can be used to provide more information about the product. The intent is to capture relevant characteristics about the product from donor and collection through the final processing. In some settings, such as where multiple additives are used, the additional information is part of the accompanying documentation, especially where label space is limited. It is not intended that products would be relabeled at the bedside, so attributes such as “thawed” would only be applied if that process occurred in the laboratory.

Labels for cellular therapy products characterized in this standardized way can be designed using common, well-defined terms that are printed in eye-readable format. The eye-readable terminology may be in the native language of the country in which the product is collected. The language also adapts to machine-readable technologies such as bar codes. In this way, the products will be universally understood and international exchange will be facilitated.

The standard terminology is structured in a manner that allows revisions, additions, and deletions as necessary on a continuous basis. In this edition of Standards, the common major classes of products are defined as was current at the time of publication. Modifications in definitions and additions will occur. As the responsible body for the database development and maintenance, ICCBBA is the appropriate authority for maintaining publications on current terminology. Facilities must use the terminology as defined in the ICCBBA document *Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions*, which is available at www.iccbba.org > Subject Area > Cellular Therapy > Standard Terminology. CBBs should refer to Chapter Three, Cellular Therapy, for current terms and definitions related to cellular therapy. Inspectors will inspect the CBBs according to the current ISBT 128 terminology and definitions.

If CB Processing Facilities have questions regarding ISBT 128 terminology, they can reference the Standard Terminology document, view the ICCBBA website at www.iccbba.org, or contact ICCBBA directly for additional information and assistance. The website also includes resources and tools for identifying and assigning standardized codes for cellular therapy products or requesting a code for a new unique product.

Evidence:

Inspectors will examine the labeling process and procedures to verify the appropriate use of ISBT 128 terminology is in use with the regard to class and attributes. Inspectors should review Chapter Three, Cellular Therapy in the ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions (available at www.iccbba.org) before conducting an inspection. It would be helpful to have the document available for reference during the inspection as well.

STANDARD:

B6.1.2 If coding and labeling technologies have not yet been implemented, the CBB shall be actively implementing ISBT 128.

Explanation:

A plan to implement ISBT 128 usage, including technology, was mandatory in the fifth edition of the Standards. In the sixth edition, active implementation for ISBT 128 coding and labeling within the CBB is required. ISBT 128 implementation is supported by FACT and numerous other organizations in the field for cellular therapy. On the ICCBBA website (<http://www.iccbba.org>), the most recent versions of the terminology are published, as are resources to help centers implement ISBT 128.

Although ISBT 128 implementation does require significant human resources to qualify vendors and equipment; validate processes; and update labels, policies, and procedures, significant capital outlays are not expected. Facilities will be required to pay a fee to ICCBBA and purchase software, label printers, and possibly laptops if that would facilitate new print-on-demand processes.

Evidence:

Inspectors will expect to see active development of ISBT 128 labels, printers, software, etc. and documentation of associated staff training and validation. Organizations must demonstrate a clearly documented infrastructure including:

1. Registration with ICCBBA.
2. Identification or creation of appropriate product codes.
3. Label designs according to the requirements of ICCBBA for Cellular Therapy Products.
4. Label validation.
5. Use of scanned information at the time products are received and at distribution from the CB Processing Facility.

It is understood that some organizations may have difficulty with active implementation early after the effective date of these standards. Organizations may be requested to provide updates throughout the accreditation cycle via interim reporting. Organizations that have implemented ISBT 128 coding and labeling technologies within the facility meet the requirement.

Example(s):

ISBT 128 is compatible with the Single European Code for Tissues and Cells (Eurocet 128).

STANDARD:

B6.2 Label Controls.

B6.2.1 A system for label version control shall be employed.

Explanation:

The document control system used for various parts of the label and what constitutes a label version must be defined by the facility or program. Any change in the label or label element that would change the interpretation of the label information would constitute a version change. The version number does not have to be on the label but should be on each label template at a minimum.

Example(s):

Labels may 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. For example, labels used for related CB donations should be clearly segregated from those used for unrelated CB units.

STANDARD:

B6.2.1.1 Previous versions of labels shall be archived indefinitely.

Explanation:

Labels are controlled documents and need to be archived for reference. For on-demand labels, the template and an example demonstrating conformance with the template should be archived. Obsolete labels should be archived for as long as the current CB inventory has the labels.

STANDARD:

B6.2.2 A system for label reconciliation shall be employed.

Explanation:

The CBB must account for all labels created. Several labels related to a single CB unit are typically created to use on the unit bag itself, on samples, on documentation, etc. Accounting for how many labels are applied to a specific unit and its samples, how many have been destroyed, and how many remain in the file provides assurance that labels have not been inappropriately applied either to that particular unit or to another. Any label with a specific identifier needs to be accounted.

Example(s):

A CBB could designate labels for each step in the process to minimize risks of mislabeling by beginning with 24 labels. Three (3) are used for original, in-process, and final CB units, nine (9) are used for ancillary samples, six (6) are applied to paperwork, and three (3) are involved in reference lab submissions. Its process should indicate that the remaining three (3) are retained in the unit file or discarded.

STANDARD:

B6.2.3 The label shall be validated as reliable for storage under the conditions in use.

Evidence:

The results for validation studies of the labels under the conditions in use, including cryopreservation and storage, must be available to the inspector.

STANDARD:

B6.2.4 Pre-printed labels.

B6.2.4.1 Labels shall be held upon receipt from the manufacturer pending review and proofing against a copy or template approved by the CBB Director or designee to confirm accuracy regarding identity, content, and conformity.

Explanation:

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

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

The CBB Director may designate the approval of labels to a suitable, qualified person but maintains ultimate responsibility.

Example(s):

The CBB Director may designate the approval of labels to someone from the CBB's Quality Unit.

STANDARD:

B6.2.4.2 Stocks of unused labels representing different products shall be stored and maintained in a controlled manner to prevent errors.

B6.2.4.3 Unused obsolete labels shall be destroyed.

Explanation:

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 indefinitely.

STANDARD:

B6.2.5 Print-on-demand label systems shall be validated to confirm accuracy regarding identity, content, and conformity of labels to templates approved by the CBB Director or designee.

Explanation:

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.

The CBB Director may designate the approval of labels to a suitable, qualified person but maintains ultimate responsibility.

Example(s):

The CBB Director may designate the approval of labels to someone from the CBB's Quality Unit.

STANDARD:

B6.3 Labeling Operations.

B6.3.1 Labeling operations shall be conducted in a manner adequate to prevent mislabeling or misidentification of CB units, samples, and associated documents.

Explanation:

Labeling operations must effectively allow the CBB to maintain the relationship between the CB unit and its samples and records. Applying the correct labels to units, samples, and documents is critical to accurately link test results, documentation, and donors.

The labeling SOPs should indicate that there are procedures in place for the items listed in the substandards to B6.2, including at a minimum:

- Receipt and quarantine,
- Verification of accuracy,
- Proper storage,
- Version control, and
- Destruction of obsolete labels.

Evidence:

Examples of all labels in use by the applicant CBB, including partial and in-process labels, will be provided to the inspector prior to the on-site inspection. Label content will have been pre-reviewed by the FACT office staff. On site, the inspector will verify that the labels submitted are in fact the labels in use at the facility. The inspector will focus more time on the labeling process, specifically assessment of its adequacy with respect to proper identification of CB units, samples, and related documents. The inspector will observe the location where labels are stored to verify that the labels are organized in a manner to prevent errors.

STANDARD:

B6.3.2 There shall be processes to verify that all labels in use are accurate, legible, and maintain physical integrity.

B6.3.2.1 A system of checks in labeling procedures shall be used to prevent errors in transferring information to labels.

B6.3.2.2 A controlled labeling procedure consistent with Applicable Law shall be defined and followed if container label information is transmitted electronically during a labeling process. This procedure shall include a verification step.

Explanation:

This standard requires facilities to have a careful process for electronically transmitting information (such as with a bar code) and to double check the information rather than becoming solely dependent on the technology to work correctly.

Evidence:

For systems using computer-assisted label verification to confirm label accuracy (such as bar-code scanning), procedures and records should show how the automatic verification works.

STANDARD:

B6.3.2.3 When the label has been affixed to the CB unit bag, a sufficient area shall remain uncovered to permit inspection of the contents.

Evidence:

The inspector will examine labeled CB units on-site to verify that labels are firmly attached or affixed and that sufficient area of the unit remains uncovered to allow examination of contents. Label elements that are required by governmental regulation must be clearly visible and any additional label requirements of Applicable Law must be present.

STANDARD:

- B6.3.2.4 Information on the CB unit being labeled shall be verified, prior to allowing the CB unit to progress to the next stage of processing, storage or distribution, by one (1) qualified staff member using a validated process or by two (2) qualified staff members.*
- B6.3.2.5 All data fields on labels shall be completed.*
- B6.3.2.6 All labeling shall be clear, legible, and printed using ink that is indelible to all relevant agents.*

Explanation:

Ink used on labels must be indelible to relevant agents used in the process of CB banking. Indelible ink must also be used to record any information entered manually on the label. All data fields on a label must be complete; fields for which information is not required must be completed as not applicable or "NA." Labels must have been validated to confirm they remain legible under the conditions in which they are used. This is of particular importance for labels used on cryopreserved CB units.

Example(s):

Relevant agents include liquids such as liquid nitrogen, alcohol wipes, and other liquids used around CB units.

STANDARD:

- B6.3.2.7 Labels affixed directly to a CB unit bag shall be applied using appropriate materials as defined by the applicable regulatory authority.*
- B6.3.3 CB units that are subsequently re-packaged into new containers shall be labeled with new labels before they are detached from the original container.*
 - B6.3.3.1 The process to establish linkage between original and new labels shall be validated.*
 - B6.3.3.2 This linkage shall be maintained as a permanent part of the CB unit record.*

Evidence:

If CB units are repackaged, the CBB needs to be prepared to demonstrate that there are mechanisms in place (either on the label itself or via accompanying paperwork) to trace the unit from its origin to the final disposition.

STANDARD:

B6.3.4 Integrally attached segments should be labeled with an identifier linking the segments to the applicable CB unit.

Explanation:

CBBs should be actively implementing a process to add an identifier to integrally attached segments, linking the segments to the applicable CB unit.

STANDARD:

B6.4 Identification.

B6.4.1 There shall be a human-readable system and a machine-readable system in operation for identification of the CB unit, samples, and associated documents.

Explanation:

In addition to a machine-readable system, a human-readable component must also be included in case a scanner breaks and prevents machine-reading ability.

STANDARD:

B6.4.2 Each CB unit shall be assigned a unique numeric or alphanumeric identifier by which it will be possible to trace any CB unit to its maternal and infant donor data, delivery information, family history, test results, and to all records describing the handling and final disposition of the CB unit.

B6.4.2.1 There shall be processes to ensure that the CB unit identifier is unique to prevent errors in identification.

B6.4.2.2 If a single CB collection is stored in more than one fraction, there shall be a system to identify each fraction.

B6.4.2.3 For multiple gestation deliveries, there shall be a system to link each infant donor to the correct CB unit.

Explanation:

The unique identifier at the end of collection is not required to be the permanent barcode identifier that is assigned by the CBB. The combination of elements used to create a unique identifier may vary in different regions of the world where common names and birth designations may be inadequate. The elements chosen to create the unique identifier should be appropriate to the culture and region, and may not be the same from one bank to another. If the maternal name, medical record number, or dates of birth are used, they should not be observable by the courier or general public during transport to the facility where the permanent identifier is assigned.

It is permissible to assign the permanent unique identifier to the CB unit at the time of collection if it is done in a centralized and controlled process. However, barcode labeling may be more easily controlled when performed at the CB Processing Facility rather than at the CB Collection Site where maternal identifiers are much more familiar. The combination of mother's name, medical record number, and date of birth is unique in the environment of the CB Collection Site. This information may be used to provide linkage between the donor and the subsequent unique identifier assigned by the CBB. There is some opportunity for error when pre-labeling tubes and bags for the CB Collection Site in hospital-based collections. A kit assembled for one delivery may be separated for use during another delivery, in which case multiple identifiers could be used for the collection of one unit and possibly prevent banking.

If a CBB uses multi-compartment bags for CB units, the identification system must be validated to confirm each fraction is identified during all stages of unit manufacturing.

Example(s):

The term "unique" refers to an identifier that is not used for anything else; for example, the following (each used alone) would not be considered to be a unique identifier for a CB unit: the medical record number used to identify a patient or mother of the infant donor, the medical record number used to identify the infant donor at the hospital, or a Social Security Number in the U.S.

Name, medical record number, and birth date may be used in a unique combination at the end of collection but must be linked to another identifier at least upon receipt into the CBB. For reasons of confidentiality (per FDA 21 CFR 1271.290(c) and 1271.55(a)(1)), once a donor eligibility determination has been made, U.S. CBBs may not use name, social security number, or medical record number as part of the unique identifier.

STANDARD:

B6.4.3 If the CBB designates an additional or supplementary numeric or alphanumeric identifier to the CB unit or samples, supplementary identifiers shall not obscure the original identifier.

B6.4.3.1 The facility associated with each identifier shall be documented.

B6.5 The information provided on the label by the CB Collection Site shall be maintained indefinitely as part of the CB unit record.

B6.6 Label Content.

B6.6.1 The content of each label shall be compliant with Applicable Law and these Standards.

Explanation:

Label elements required by Applicable Law must be included, and information in addition to the required elements in Appendix II may be necessary accordingly.

Example(s):

For U.S. CBBs that wish to submit a BLA, the U.S. FDA guidance, "Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications," outlines specific regulations that apply to the label content for prescription drug products.

STANDARD:

- B6.6.2 *Each label shall include at least the required information detailed in the Cord Blood Unit Labeling table in Appendix II.*
- B6.6.3 *Each label shall be accompanied by the appropriate biohazard and warning labels as found in the Circular of Information for the Use of Cellular Therapy Products, "Table 2. Biohazard and Warning Labels on Cellular Therapy Products Collected, Processed, and/or Administered in the United States" or other appropriate labels required by Applicable Law.*

Explanation:

The receiving facility address should be complete enough to ensure receipt of the CB unit at the CB Processing Facility.

The time zone is included in Appendix II for those CBBs that collect at CB Collection Sites outside the time zone of the CB Processing Facility. This information has bearing on the time in transit, time to processing, and time to cryopreservation.

Additives refer to any solutions added to the CB unit, including anticoagulants, sedimenting agents, and cryopreservation solutions. Even though the contribution of these additives may be minimal post processing, it is important that the transplant physician and recipient are aware of their presence to prevent or minimize a reaction to the infusion in the event that the recipient has a known allergy to an additive.

Date and time of distribution and the statements "Handle With Care" and "Medical Specimen" are required by European Directive. Since these are international standards and CB units can be distributed to Europe, assuring global compliance is reasonable.

A biohazard label must be attached or affixed to any CB unit from which a donor sample has tested positive for a relevant communicable disease (excluding CMV) or when donor screening indicates a risk factor for a relevant communicable disease or disease agents. Table 2 of the inter-organizational Circular of Information for Cellular Therapy Products outlines when biohazard labels must be used. Biohazard labels can only be applied to units not required to be labeled biohazard when specific circumstances for their use are defined by policy. Biohazard labels must not be applied indiscriminately. These labels are meant to denote a greater hazard than that posed by any biological product. Using biohazard labels on all units without rationale that is documented in facility records is considered a deficiency unless such use is required by Applicable Law.

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 in the U.S. as interpreted at some institutions. 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 safe to prevent transmission of infectious disease.

Warning labels are required when CB unit testing or screening is positive for infectious disease risk or is incomplete. The exact statements that are required differ for autologous and allogeneic products. Table 2 of the inter-organizational Circular of Information for Cellular Therapy Products details the circumstances under which these warnings are required.

The labeling applies to the travel restrictions in effect at the time of collection. Although there may be a risk associated with prolonged incubation period of virus in countries added to the list post collection, that risk is considered minimal.

When a CB unit is shipped (such as by truck or airplane without trained personnel), statements such as “Do Not X-Ray,” “Medical Specimen,” “Handle with Care,” and shipper handling instructions must be affixed to the outer container. This includes units shipped from a remote CB Collection Site to a CB Processing Facility or from the CBB to a Clinical Program.

Evidence:

The inspector will verify that biohazard labels and warning statements are utilized as described in Table 2 of the inter-organizational Circular of Information for Cellular Therapy Products. The current version is posted on the FACT website at <http://www.factwebsite.org> > Education and Resources > Resources. CBBs that are licensed with regulatory authorities may have requirements additional to those outlined in this table.

Autologous and allogeneic product labels must have the statement “Not Evaluated for Infectious Substances” present when the donor screening does not include all of the elements required by Applicable Law.

The CBB must show the inspector CB unit labels for units distributed under an IND and under a BLA, as applicable, to demonstrate the appropriate statements are used on the unit or in the accompanying documents issued with the unit. The inspector will verify that CB units are distributed with the required statement on the label or in the accompanying records.

Example(s):

There are a number of mechanisms to comply with the requirement to label CB units as biohazardous:

- When an infectious risk is determined by testing that was not completed at the time of cryopreservation, a CBB may choose to attach a biohazard label to the unit and maintain it in quarantine storage. However, for units frozen with overwrap, attaching a tie tag can be impossible, and that information should accompany the unit.
- When infectious disease testing is positive and the CB unit is retained, some CBBs may elect to place the biohazard label in the accompanying records.

Per FDA donor screening requirements, CB units are ineligible if communicable disease testing was performed in a non-CLIA certified lab or if the donor is a resident of a country in the USDA BSE list. A list of countries at risk can be found at <http://factwebsite.org/Inner.aspx?id=742>.

CB units that are regulated under the U.S. FDA 351 regulations must be either distributed under a BLA or an IND. Licensed CB units must have a National Drug Code (NDC). If distributed under an IND, the unit must be labeled with the statement “Caution: New drug limited by federal law for investigation use only.” Such CB units must contain this statement attached or affixed to the label or accompanying the unit.

The label or accompanying records for licensed CB units must include the statement “Rx Only” indicating that the unit may only be distributed by a prescription from the transplant physician. The physician order form required by these Standards may serve as the prescription.

Labeling requirements for the UK can be found in the *Guide to Quality and Safety Assurance for Tissues and Cells for Patient Treatment*. This guide is available at:
[http://www.hta.gov.uk/db/documents/Annex - Guide to Quality and Safety Assurance for Tissues and Cells for Patient Treatment.pdf](http://www.hta.gov.uk/db/documents/Annex_-_Guide_to_Quality_and_Safety_Assurance_for_Tissues_and_Cells_for_Patient_Treatment.pdf).

Canadian labeling requirements can be found in the *Guidance Document for Cell, Tissue and Organ Establishments - Safety of Human Cells, Tissues and Organs for Transplantation* at http://www.hc-sc.gc.ca/dhp-mps/brgtherap/reg-init/cell/cto_gd_ld-eng.php.

STANDARD:

B6.6.4 *A partial label at a minimum shall be attached to the CB unit during all stages of processing.*

B6.6.5 *CB units with an attached partial label shall be accompanied by required information enclosed in a sealed package as detailed in the Cord Blood Unit Labeling table in Appendix II.*

Explanation:

A minimum of a partial label is required on the CB unit. Additional information may be attached to the unit via a tie tag or be present on accompanying paperwork. It is not acceptable to transport multiple units from different donors using partial labels in a single container or with all of the additional information on a single inventory sheet.

Only the CB unit needs a partial label; other samples do not require a partial label but must have at least some identifier.

In CBBs where both related and unrelated banking occurs, CB units collected for related use must be labeled in a manner that obviously and immediately separates them from the unrelated allogeneic inventory to ensure that a related unit is not available for unrelated use.

Evidence:

If the CBB uses a partial label at any stage in collection, distribution, processing, cryopreservation, or storage, the CBB must show the inspector the labeling SOP describing the use of that partial label, an example of the partial label, and the process for providing the additional information that is not included on the partial label.

Example(s):

Though the CB unit may transiently occupy a syringe during a transfer from one container to another, the syringe itself would not be considered the actual CB unit. So long as it is a mechanism used to transfer the CB unit, bearing just the unique identifier is sufficient.

B7: EQUIPMENT

STANDARD:

B7.1 *All critical equipment shall be defined, qualified, and validated for the intended use.*

B7.1.1 Equipment should be used in accordance with the manufacturer's instructions.

Explanation:

Qualification of equipment establishes confidence that it functions consistently within established limits. However, the manner in which equipment is used must also be validated.

Example(s):

A change in equipment to a new controlled rate freezer might require qualification of the freezing program to confirm that the freezing parameters meet the predetermined specifications. A validation study may be performed by freezing CB units under the parameters to be used to preserve viability of the CB units.

Although critical equipment should be installed per manufacturer's guidelines and IQ, PQ, and OQ performed and documented, some equipment (e.g., particle counter and cell counters) may require repurposing from the initially designated biological samples. For example, a particle counter and cell counters may have been designed by manufacturers to enumerate nucleated cells and nucleated red blood cells in EDTA anticoagulated peripheral blood, and equipment error messages may result when used to count these cells in cord blood. Since total nucleated and mononuclear cell counts are utilized by Clinical Programs to choose CB units, the CBB should confirm the accuracy of the counts by using other analytical methods, for example, microscopy or flow cytometry.

STANDARD:

B7.2 Equipment shall be used in a manner that prevents CB unit mix-ups, contamination, and cross-contamination, and that does not compromise unit function and integrity.

Explanation:

While it cannot be guaranteed that the viability will not be affected or that adventitious agents will not be introduced, a CBB can take reasonable precautions to prevent or limit the occurrence. Every effort must be made to ensure that equipment used does not alter the viability of the CB unit, allow for introduction of adventitious agents, or transmit or spread communicable disease. Initial qualification of equipment, validation for its intended use, and periodic audits will help confirm that the equipment is performing as required. If there is an occurrence of introduction of adventitious agents or the transmission or spread of communicable disease, the CBB should investigate, report, and prevent future occurrences through its corrective action policies.

STANDARD:

B7.3 Equipment records shall include the manufacturer's name, serial number or other identifier, manufacturer's instructions, equipment location, and use of each piece of equipment, including the identification of each CB unit for which the equipment was used.

Example(s):

If the CBB can demonstrate traceability of the equipment identification within the CB unit records, documenting for which CB unit the equipment was used within the unit records is acceptable. The CBB should consider how it will identify which units were affected by an issue with equipment in a manner that will allow for expediency and accuracy.

Although this approach complies with the Standards, it is not acceptable for U.S. BLAs. All records must be in each CB unit record.

STANDARD:

B7.4 Calibration.

- B7.4.1 Equipment shall be inspected, tested, and calibrated on a regularly scheduled basis as recommended by the manufacturer, after a critical repair or move, and, at a minimum, annually.*
- B7.4.2 All equipment with a critical measuring function shall be calibrated against a traceable standard, if available. Where no traceable standard is available, the basis and acceptance criteria for calibration shall be described and documented.*
- B7.4.3 When equipment is found to be out of calibration or specification, there shall be a defined process for action required for CB units manufactured since the last calibration.*
- B7.4.4 Records of the dates and copies of calibration results shall be maintained.*

Explanation:

Equipment SOPs must also describe how the equipment is operated or refer to relevant operations manuals that are available within the CBB. Maintenance and calibration are required to detect malfunctions and defects and to confirm that the critical parameters are maintained within acceptable limits at all times. There must be a schedule for equipment maintenance and quality control at minimum as per manufacturer's recommendation.

Calibration records shall be readily available near the equipment indicating that quality control (QC) parameters have been met, the date QC testing was performed, and when such testing is next due. Where applicable, calibration procedures should include limits for accuracy and precision.

Equipment identified by the CBB to have a critical measuring function, such as thermometers, timers, and scales, must be calibrated against a traceable standard. A traceable standard is one that can be directly linked to a provider that has documented the accuracy of the measuring device.

When equipment is found to be out of calibration or specification, the validity of previous measurements and decisions based on those measurements should be reviewed. There should be documentation that the CB units manufactured during this period of uncertainty have been evaluated and determined to be conforming to specification or corrective action has been documented. This should include an investigation of potential adverse events to manufactured products using the equipment tracking system. Note that if critical equipment used in processing is located outside of the CBB, such as sterilization equipment, it is the CBB's responsibility to confirm that equipment is properly maintained and calibrated.

Evidence:

Calibration records can be used to confirm that traceable standards have been used. 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 must exist. Records to document these activities, including investigation of potential adverse events caused by cellular therapy products, should be present.

Schedules may vary among CBBs, based on frequency of use, performance stability, or recommendations from the manufacturer. Recent records of regularly scheduled maintenance and QC should be readily available for each piece of equipment.

Example(s):

Examples of traceable standards include National Institute of Standards and Technology (NIST) reference thermometers, stop watches, and tachometers. Other vendors may provide similar products but they must have a direct link to records indicating accuracy to a known standard. An alternative to using the actual traceable standard is to calibrate a similar device against the traceable standard and use the newly qualified device for routine measurements. If a traceable standard cannot be obtained, then the CBB must document how the accuracy of the measurement reading was determined.

Tags or stickers on equipment are one way to document quality control (QC) for immediate reference.

STANDARD:

B7.5 Maintenance and repairs.

B7.5.1 Equipment shall be maintained in a clean and orderly manner and located so as to facilitate cleaning, sanitation, calibration, and maintenance according to established schedules.

B7.5.2 Records of the maintenance schedule; maintenance performed; and damage, malfunction, modification, or repair to equipment shall be maintained.

Explanation:

In addition to the regular maintenance schedule and maintenance after repairs, the CBB also needs to perform the necessary maintenance and repairs after moving equipment.

STANDARD:

B7.5.3 There shall be a Standard Operating Procedure that addresses the actions to take in the event of equipment malfunction or failure.

B7.6 Cleaning and sanitation.

B7.6.1 Equipment shall be cleaned and sanitized according to established schedules.

B7.6.2 Records of equipment cleaning and sanitation shall be maintained.

B7.7 Equipment shall be routinely inspected for cleanliness, sanitation, and calibration and to confirm adherence to applicable equipment maintenance schedules.

B7.8 Records of recent maintenance, cleaning, sanitizing, calibration, and other activities shall be displayed on or near each piece of equipment.

B8: SUPPLIES AND REAGENTS

STANDARD:

B8.1 Vendors for all critical reagents and supplies shall be qualified.

Explanation:

Criteria for selecting vendors for critical reagents and supplies must be written and reasons for their selection must be justified.

Example(s):

Surveys of critical vendors may be conducted to provide a description of their quality plan and operations, and to determine if the vendor can provide the necessary supplies and reagents and comply with the appropriate Standards. Depending on risk, on-site audits may be performed.

STANDARD:

B8.2 Critical reagents and supplies shall be defined and qualified to function as expected.

B8.3 Supplies and reagents shall not adversely affect the viability of the CB unit and shall not permit the introduction of adventitious agents or the transmission or spread of communicable disease.

B8.4 Supplies and reagents that come into contact with the CB unit shall be sterile.

B8.4.1 Sterilization of supplies and reagents prepared within the facility shall be documented.

B8.5 Supplies and reagents should be used in a manner consistent with instructions provided by the manufacturer.

B8.6 Supplies and reagents used for CB collection, processing, or cryopreservation, whenever possible, shall be approved for human use.

B8.6.1 Supplies and reagents shall be of the appropriate grade for the intended use.

B8.7 Certificates of analysis shall be obtained and maintained indefinitely on file for all critical reagents.

B8.8 Receipt, inspection, verification, acceptance, and storage of supplies and reagents shall be documented.

B8.8.1 The disposition of rejected supplies and reagents shall be documented.

B8.9 The lot number, expiration date, and manufacturer of supplies and reagents used for the collection and processing of each CB unit shall be documented.

Explanation:

Whenever possible, supplies and reagents that come into contact with CB units must be approved for human use. If there are no suitable supplies or reagents approved for human use, those used must be clinical or pharmaceutical grade, as appropriate, and free of microbial contamination. For simple, routine collection, processing, or cryopreservation of units, several reagents that are of clinical or pharmaceutical grade have been identified, and results of the studies utilizing these reagents have been published in the peer-reviewed medical literature for over 20 years.

Where there are no suitable clinical or pharmaceutical grade reagents available for processing, the reagents in use shall be qualified. This may include:

- Use under IND, IDE, or other exceptions approved by the appropriate regulatory agency,
- Evidence of extensive experience with the reagent and data showing that no suitable, equivalent reagent of the appropriate grade can substitute,
- Extensive literature supporting use of the reagent for the specified purpose and data showing that no suitable, equivalent reagent of the appropriate grade can substitute.

If a reagent is not of the appropriate grade, it should be of the highest grade (or purity) available, and the CBB must validate that the reagent is safe and effective for the specified purpose. Any reagents generated in-house for use in CB unit processing must be qualified and validated for their intended use.

For example, DMSO not approved for clinical use must undergo lot-to-lot functional qualification. It is a critical reagent that actually performs a function (i.e., it protects the cells themselves). Should a lot of DMSO not function as expected, there would be dire consequences to the cellular therapy product and the intended recipient.

Reagents and supplies that are received into the facility shall be examined for contamination, breakage, discoloration, etc. before they are placed into the facility's inventory and made available for use. There shall be an SOP describing this process and the results of the examination should be documented. Records must be kept of the receipt of each supply or reagent including 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 CB unit manufactured.

The inventory control system must be adequate to prevent the use of outdated or damaged supplies and reagents. 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. This mechanism can be tracked on paper or via a computer program.

Storage of supplies and reagents should be in accordance with the manufacturer's recommendations in regards to temperature, humidity, and any other storage requirements.

Evidence:

Records of reagent qualification and, if indicated, validation of its intended use must be available. Qualification may be performed by the CB Collection Site, the CB Processing Facility, or the manufacturer. In the case of manufacturer qualification, the Certificate of Analysis should be available in the facility. Records pertaining to supplies and reagents shall be maintained.

Example(s):

The definition and requirements for each critical reagent and supply may be listed on a specification sheet. Information on this sheet may include a description of the product, the catalog number, transportation requirements, required documentation (e.g., certificate of analysis), qualification checks to be performed, acceptance criteria, and storage conditions.

Verification of each new lot of cryopreservation medium may be performed by comparing post-thaw CFU or viable CD34 recovery with the current batch of cryopreservation medium.

U.S. CBBs should refer to FDA 21 CFR §1271.210 regarding supplies and reagents.

B9: INVENTORY MANAGEMENT

STANDARD:

B9.1 The inventory management system shall clearly distinguish related CB units from unrelated CB units.

B9.2 The inventory management system for CB units shall allow each CB unit and its samples and records to be located in a timely manner. The inventory records shall include:

B9.2.1 CB unit unique identifier.

B9.2.2 Maternal donor identifier.

B9.2.3 Storage device identifier.

B9.2.4 Location within the storage device.

Explanation:

Mechanisms must be in place to facilitate the retrieval of CB units and samples at any time when needed. Processes in a CBB are complicated by the fact that multiple samples of varying types and storage requirements are maintained. Furthermore, units may be in transitional quarantine until placed in permanent storage, which may dictate separate locations and necessitate transfers. Therefore, the inventory management plan must include a system of documentation and audits to confirm the system is functioning properly.

STANDARD:

B9.3 The inventory management system shall be designed to prevent mix-ups, contamination of the CB units during storage, and the improper release of CB units.

Example(s):

U.S. CBBs should refer to FDA 21 CFR 1271.260 regarding storage. These banks must keep CB units in quarantine prior to completion of donor eligibility determination and identify units from ineligible donors.

STANDARD:

B9.4 The inventory management system shall be designed to address the duration of storage for cryopreserved CB units, including assigning an expiration date to CB units where appropriate.

Explanation:

The definitive expiration date for CB units is currently unknown due to different processing and storage methods and the effects of long-term storage on unit potency. Therefore, expiration dates are not dictated by the Standards. Rather, these should be determined based on the CBB's own viability and recovery data. If no expiration date has been established, this should be documented. CBBs are required to establish policies for the duration and conditions, including validation of, storage and are encouraged to generate data to use for decision making in the future.

STANDARD:

B9.5 The CBB shall have policies related to the return of CB units to the CBB inventory.

B9.5.1 Unrelated CB units shall not be returned to the CBB inventory after they have left the CBB premises.

B9.5.2 If related CB units are returned to the CBB inventory, there shall be documentation of appropriate storage and transportation.

Explanation:

Return of unrelated CB units is not permitted in part as a protection for the CBB. CBBs must verify that the Clinical Programs are prepared to accept responsibility for the shipment prior to its release from the CBB. If a related unit is returned, the CBB must document that storage and transportation throughout the time the unit was away from the bank was within the specified parameters, including continuous temperature monitoring documentation that confirms appropriate temperature.

B10: INVENTORY TRANSFER

STANDARD:

B10.1 The CBB shall have a policy or plan for the potential transfer of all or part of the CB unit inventory.

B10.2 The procedure or plan shall require a written agreement between the transferring and accepting CBBs that describes the responsibilities of each CBB, including the elements in B10, at a minimum.

B10.2.1 The written agreement shall specify that FACT-NetCord accreditation does not transfer with the inventory.

B10.2.2 The transferring CBB shall provide the receiving CBB with all records in B10.3.3.

Explanation:

The written agreement between the transferring and accepting CBBs must describe which bank has responsibility for the elements listed in this section of the Standards. Early communication between the two banks is necessary so that all information required for future storage of the inventory is available. This communication needs to happen before the agreement is signed so that the banks are certain that the receiving bank has the records, storage space, and other requirements needed to protect the CB unit inventory.

There should be a mechanism by which the CBB Director or designee of the transferring CBB can be contacted for information regarding CB units transferred from the CBB. This period of time must be defined in the contract or agreement.

CBBs may not claim FACT-NetCord accreditation status solely because transferred CB units came from an accredited bank. Likewise, CBBs may not claim that a unit is accredited because accreditation is of bank processes only. If a FACT-NetCord accredited bank accepts nonconforming units, it must assess the quality of those units and disclose nonconformances to registries and Clinical Programs.

Example(s):

One of the requirements in this section is that the transferring CBB informs the receiving bank of the manufacturer and dimensions of the CB unit bag and canister. It is critical that this information is shared in advance in case the receiving bank does not have the freezers necessary to accommodate the units.

STANDARD:

B10.3 The procedure or plan shall require the following responsibilities of the receiving CBB:

B10.3.1 Records shall be in a language and form that can be understood by the accepting CBB personnel.

Explanation:

If the records are not in the language of the receiving CBB, they should be translated using a certified translation service.

STANDARD:

B10.3.2 There shall be documentation of review of records and of transferred inventory to verify that the CB units meet the requirements of the written agreement for transfer of inventory.

B10.3.3 Transferred records shall include at a minimum:

B10.3.3.1 Maternal consent.

B10.3.3.2 Medical and genetic history.

B10.3.3.3 A summary of records used to make the donor eligibility determination.

Evidence:

The completed medical questionnaire must be included with the medical and genetic history.

STANDARD:

- B10.3.3.4 Identity and results of all maternal communicable disease tests, and, if performed, the identity and results of all CB unit communicable disease tests.*
- B10.3.3.5 All results from testing performed on the CB unit.*
- B10.3.3.6 Processing records.*
- B10.3.3.7 Cryopreservation records, including program parameters and freezing curve detailing each step of the freezing process.*
- B10.3.3.8 The manufacturer and approximate dimensions of the storage bag and canister.*
- B10.3.3.9 Number of attached segments and other samples.*
- B10.3.3.10 Other records as required to allow the receiving CBB to meet these Standards.*
- B10.3.4 There shall be a Standard Operating Procedure for inspecting incoming CB units for damage and contamination.*
- B10.3.5 After the CB units have been transferred, but before the transferred inventory is made available for search:
 - B10.3.5.1 The integrity and viability of CB units shall be verified to confirm the transport or shipping method did not compromise CB unit viability.**

Explanation:

The CBB must verify the transport or shipping method did not compromise CB unit viability. To do this, the CBB can set up a study using a sampling of units that were all handled in the same manner.

STANDARD:

- B10.3.5.2 There shall be confirmation of the completeness of all records described in B10.3.3.*
- B10.3.5.3 The accepting CBB shall determine whether to accept, reject, or place in quarantine incoming CB units based on established criteria designed to prevent the transmission of communicable diseases.*

B11: DOCUMENTS AND RECORDS REQUIREMENTS

STANDARD:

- B11.1 Employee records shall be maintained in a confidential manner as required by Applicable Law.*
- B11.2 A record management system shall be established and maintained to allow for protection, preservation, integrity, disposal, and ready retrieval of records.*
- B11.2.1 Records shall be available for inspection by authorized individuals upon request from a regulatory or accrediting agency.*
- B11.3 If records are maintained in more than one location or format, there shall be a system for prompt identification, location, and retrieval of all records.*

Explanation:

Each CBB 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 allow prompt identification, location, and retrieval of all records. The methods for filing and transfer of records to archival storage should be specified in an SOP.

Electronic records must be backed up on a regular basis and stored to prevent their loss. In the event that the CBB ceases operation, it must make provisions for all records to be maintained for the required period.

Records include quality control, personnel training and competency, facility maintenance, facility management, and other general facility records.

Facility maintenance records include documentation of dates and extent of repairs on mechanical systems, dates and extent of renovations and new construction; preventive maintenance on equipment; personnel responsible for cleaning; additional training records when required; and the outcome of any building or facility inspections for safety or compliance with governmental 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.

Not all records must be immediately available; availability at an off-site storage is acceptable.

Evidence:

It is suggested that CBBs have a minimum of the previous three years' records readily accessible to the inspector for review.

Example(s):

It is recommended that recent records should be kept on-site and archived records should 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, copying, or printing records maintained electronically using devices such as microfiche or microfilm.

STANDARD:

B11.4 Identity and medical records of the infant donor and family shall be in a language understood by the CBB personnel, registry, and/or Clinical Program.

B11.4.1 Records of exported CB units shall be in a language understood by the importing organization or shall be translated to English and accompanied by a statement of authenticity by the translator prior to release of the CB unit.

B11.5 The following CBB records shall be maintained indefinitely:

Explanation:

Indefinite does not necessarily mean permanent. Indefinitely is defined as a timeframe without a fixed or specified limit. CB banking is a young field in which CB units could conceivably be stored indefinitely given the lack of consensus on expiration. The standard requiring indefinite storage of associated records that describe the manufacture of a unit is intentionally conservative. For example, if a CBB released a unit that has been stored for 15 years, it is likely that many things have changed, such as processing methods, equipment, and consent forms. Because review of these records is required for release of the unit and review of any resulting adverse events, it is important to retain the information.

Example(s):

U.S. CBBs should refer to FDA 21 CFR 1271.270(b) setting forth requirements for records management systems.

Records of CB units manufactured in or exported to the U.S. shall be in English or, if in another language, shall be translated to English and accompanied by a statement of authenticity by the translator prior to release of the CB unit.

STANDARD:

B11.5.1 Infant donor and parental records.

Explanation:

These include all records in Section C of these Standards. Donor files (either electronic or hard copy) must be maintained with a secure system that is designed to guarantee absolute confidentiality and is in compliance with U.S. HIPAA regulations, or applicable equivalent confidentiality and privacy regulations. The inspector should be alert to breaches in policy that potentially compromise donor confidentiality.

This standard relates to records relevant to performing donor eligibility determination, including donor screening, testing, and eligibility determination records.

STANDARD:

B11.5.2 CB unit records related to collection, processing, storage, and distribution.

Explanation:

The CB unit record includes all records related directly to the collection, processing, testing, banking, selection, and release of CB unit, including research protocols. It shall be maintained and organized in such a way as to facilitate review of the CB unit history before making it available for distribution and, if necessary, subsequent to the CB unit's release as part of a follow-up evaluation or investigation. If records are maintained in more than one location, the records management system shall be designed to allow prompt identification, location, and retrieval of all records.

The supplies and reagents used during CB unit collection or processing must be recorded. If the supplies and reagents are provided by the CBB in a kit, the kit should be identified. If the supplies and reagents are provided to contracted facilities in bulk, there should be a mechanism to identify the individual supplies and reagents used for each individual CB unit, including the manufacturer, supplier, lot number, expiration date, date of receipt, and relevant verification.

In CBBs where kits are supplied to the CB Collection Site, it is the responsibility of the CBB to maintain records of reagents and supplies provided. If the CBB provides supplies or reagents to CB Collection Sites or contracted CB Processing Facilities, the CBB must maintain records for all materials distributed.

All records are not required to be in every location where CBB activities occur. However, the CBB facility must have a mechanism to control and access all records, regardless of where the activity occurs.

STANDARD:

B11.5.3 QM records.

Explanation:

QM records include, but are not limited to, the results of audits, errors, accidents and adverse reactions reports, and outcome analysis.

STANDARD:

B11.5.4 Personnel records.

Explanation:

Personnel training and competency records include qualifications, licenses, certifications, initial training documents, and competencies for cognitive and procedural skills.

Evidence:

The CBB is responsible for keeping training and competency records related to CB collection procedures for all individuals who perform collection. If a collector is not employed by the CBB, records unrelated to collection are not required.

Example(s):

Records of collection staff training and competency may be located at the CB Collection Site or at the CBB, but must be readily available for review. If the collection staff records are not stored at the CBB, there must be an agreement to transfer these records to the CBB if the retention policies differ.

STANDARD:

B11.6 Facility cleaning and sanitation records shall be retained for three (3) years at a minimum.

Explanation:

The minimum retention period of three years is based upon the U.S. FDA's GTP requirements.

STANDARD:

B11.7 Equipment maintenance, inspection, calibration, and cleaning records shall be retained indefinitely.

B11.8 Records in case of divided responsibility.

B11.8.1 If two (2) or more facilities participate in donor management or the collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, or distribution of the CB unit, the records of each facility shall plainly show the extent of its responsibility.

B11.8.2 The CBB shall maintain a listing of the names, addresses, and responsibilities of other facilities that perform manufacturing steps on a CB unit.

B11.8.3 There shall be a system to allow the CBB access to information that tracks all manufacturing steps performed by other facilities.

B11.8.4 Each participating facility shall furnish to the facility of final disposition a copy of CB collection and processing records related to the safety of the CB unit.

Explanation:

Records may be as general as naming the facility that collected the CB or as specific as the staff member performing phlebotomy for IDM specimens, physical assessment for risk factors, and performing the actual CB collection. This is described in the CBB's policies and can be verified through a tracing approach to inspection.

STANDARD:

B11.9 Electronic Records Requirements.

B11.9.1 The CBB shall establish and maintain a current listing of all critical electronic record systems. Critical electronic record systems shall include at a minimum systems under the control of the CBB that are used as a substitute for paper, to make decisions, to perform calculations, or to create or store information used in critical procedures.

Explanation:

The definition of an electronic record is, "A record or document consisting of any combination of text, graphics, or other data that is created, stored, modified, or transmitted in digital form by a computer." This Standard requires CBBs to establish and maintain a current listing of all critical electronic record systems specific to CB banking. As CBBs utilize more electronic systems, it is important that they maintain a list of which ones are critical.

Electronic records are considered critical when they are:

- used in lieu of paper,
- used to make decisions based upon the data stored or created by the electronic record system (including outcome analysis),
- used to make calculations via automated functions,
- used to create or store pieces of information that are inputs into critical processes (whether the electronic record system is used during critical processes or used as source data for critical procedures).

It is not the intent of the Standards to include hospital-based systems and clinical medical records. These systems are typically inspected by hospital-based regulatory and accrediting organizations. Furthermore, CBBs may not have the authority to direct validation studies on these systems.

Evidence:

The CBB's list of critical electronic record systems must include all electronic record systems used by the CBB that meet the criteria in this standard.

Example(s):

Critical electronic record systems may include commercial software, custom-made software, or databases and spreadsheets.

When computers are used to generate paper printouts of electronic records, and the printouts are the "official" records used for the performance of further activities, the electronic records are not considered to be used in lieu of paper records. For example, an electronic record of the location of a CB unit in liquid nitrogen storage is printed for the unit record and the information is verified by a signature or initials. This printed record is then used by personnel to retrieve the unit at the time of infusion. The electronic record is not considered to have been used in lieu of a paper record, and may not be critical based on that criterion. If, however, the electronic system performed one or more calculations on the entered data prior to making the final printout, then the system is critical, and the standards in this section would apply. Similarly, if the electronic system formats data that is entered into a specific format for printing for retention, then that data is also processed, and validation that the data is being correctly reproduced is necessary.

If a computerized system (word processor) is used to generate SOPs, validation is not required since the quality and safety of a CB unit would not be directly affected. However, if a computerized system is used to make a critical calculation (e.g., CD34 cell recovery) and the electronic calculation is the only calculation performed, validation is required to assure that the calculation is always performed correctly under any circumstances. However, if the computerized calculation is used to confirm a manual calculation, and the manual calculation is used for manufacturing purposes, the extent of validation need not be as extensive as in the previous example.

In the U.S., when electronic records are used in lieu of paper, the inspector should refer to the FDA document Part 11, Electronic Records; Electronic Signatures - Scope and Application, for guidance to assess the validation procedures

<http://www.fda.gov/RegulatoryInformation/Guidances/ucm125067.htm>

STANDARD:

- B11.9.2 For all critical electronic record systems, there shall be policies, procedures, and system elements to maintain the accuracy, integrity, identity, and confidentiality of all records.*
- B11.9.2.1 There shall be a means by which access to electronic records is limited to authorized individuals.*
- B11.9.2.2 There shall be protection of the records to enable their accurate and ready retrieval throughout the period of record retention.*
- B11.9.2.3 All critical electronic record systems shall ensure that all donor and CB unit identifiers are unique.*
- B11.9.3 For all critical electronic record systems, there shall be an alternative system for all electronic records to allow for continuous operation of the CBB in the event that critical electronic record systems are not available. The alternative system shall be validated and CBB staff shall be trained in its use.*
- B11.9.4 For all critical electronic record systems, there shall be written procedures for record entry, verification, and revision.*
- B11.9.4.1 A method shall be established or the system shall provide for review of data before final acceptance.*
- B11.9.4.2 A method shall be established or the system shall provide for the unambiguous identification of the individual responsible for each record entry.*

Explanation:

Personnel must be trained to appropriately use all critical electronic record systems (including record entry, verification, and revision) and back-up processes when the critical systems are not available. This training must be continuous, including initial training and ongoing training as procedures are revised and issues with the use of critical electronic record systems are identified.

The final review and acceptance of entered data does not require a second individual to verify the data, nor does the identification of individuals responsible for record entries need to be automated. The intent of the standard is to require all data to be verified as correct and to require maintenance of documentation of who has entered pieces of information.

Unambiguous identification is necessary not only for record creation, but also changes to existing records. Such identification provides an audit trail useful for investigation into adverse events and deviations.

In case of error or ambiguity, a method must exist to allow traceability of data entered into the electronic record system to the staff member who performed the entry. This may take the form of an audit trail maintained internally by software, or may take the simple form of a log-in sheet on which staff members record their session with the electronic record system and identify what data was entered in that session.

Example(s):

To identify individuals responsible for record entries, several options exist. Examples include using a sign-in sheet when using the system or using a worksheet to create an audit trail of each data element. More sophisticated systems usually have an automated system that tracks record entry based upon an individual's login credentials.

STANDARD:

B11.9.5 For all critical electronic record systems, there shall be the ability to generate true copies of the records in both human readable and electronic format suitable for inspection and review.

B11.9.6 For all critical electronic record systems, there shall be validated procedures for and documentation of:

Example(s):

The FDA guidance titled, *General Principles of Software Validation; Final Guidance for Industry and FDA Staff* (2002) provides recommendations for validating electronic record systems. This guidance is available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085371.pdf>

Some CBBs have Information Technology (IT) departments that manage the electronic record system. The inspector can confirm compliance with many of these standards by talking to representatives from that department if necessary.

STANDARD:

B11.9.6.1 Systems development including the verification of calculations and algorithms.

B11.9.6.2 Numerical designation of system versions, if applicable.

B11.9.6.3 Prospective validation of system, including hardware, software, and databases.

B11.9.6.4 Installation of the system.

B11.9.6.5 Training and continued competency of personnel in systems use.

Explanation:

It is critical that the current version of the policies and SOPs be available to the CBB personnel at all times. Electronic versions are acceptable, but the CBB must have plans for management of computer system down time and document control and a method to access them must be available at all times, even in power failure.

STANDARD:

B11.9.6.6 Monitoring of data integrity.

B11.9.6.7 Back-up of the electronic records system on a regular schedule.

B11.9.6.8 System maintenance and operations.

B11.9.7 All system modifications shall be authorized, documented, and validated prior to implementation.

Explanation:

This standard is not meant to require CBBs to assume responsibility for hospital-wide data systems. Any data system that does exist within the scope of control of the CBB is required to meet these Standards.

Establishment of an electronic record keeping system that meets one or more of the criteria for a critical electronic record system requires validation. The extent of validation is somewhat dependent upon whether the computerized system was developed in-house, custom-built by an outside vendor or consultant, or developed from off-the-shelf software.

Each CBB must determine in advance whether the staff will depend on an electronic record or a paper record system to perform a regulated activity. This determination should be documented for all records created and maintained by the facility.

Validation of systems development should include:

- Documentation of development requirements and function.
- Verification that calculations are performed correctly.
- Evidence that records reproducibly contain the desired information.
- Tests of system functions under “worst case” scenarios such as system overloads (e.g., too many simultaneous users, too many simultaneous processes being performed, too many programs open on a Windows desktop), power failures, etc.
- A method for data verification before final entry.
- Internal consistency checks to verify that values are within defined ranges.
- Restricted entry of data to match predefined value limits.
- Regular quality audit trails.

As with all other cellular therapy processing activities, the staff members who utilize the electronic record system must be trained for such use. Moreover, just as SOPs are required for cell manipulations, SOPs must also be in place to describe how to enter, process, and retrieve data using the electronic record system. Competency of staff using the system must be documented on a regular basis (annually at a minimum), and must also be documented with changing versions of the systems in use.

Evidence:

The inspector will determine the scope of electronic records used by the CBB and any circumstances where the electronic record is used in lieu of a paper record.

While details of the validation system may be located in an institutional department of information services or elsewhere, the CBB shall have a summary of the validation available to the inspector.

If electronic records are used in addition to paper records, the inspector will evaluate the electronic record system to determine that:

- SOPs exist to describe the development, validation, testing, training, use, modifications, maintenance, and document control regarding the electronic system.

- The system limits access to authorized individuals and that documentation is generated to identify which individuals have accessed the system and made record entries.
- Operational system checks are performed periodically.
- Authority checks are performed periodically.
- Device checks are performed periodically.
- Documentation that the individuals performing the development, maintenance, or use of electronic systems have the education, training, and experience to perform the assigned tasks.
- Procedures are in place to provide for record keeping in the event of failure of the electronic record system, and that the staff members who may have to follow these procedures are trained in their use.
- A process for generating back-ups of records maintained electronically is in place.

B12: INTERRUPTION OF OPERATIONS AT ESTABLISHED SITES

STANDARD:

B12.1 The CBB shall have a policy or plan for the potential discontinuation of any CB collection or processing function for a period exceeding six (6) months that includes documentation of training and continued competency of all staff to perform the duties assigned upon resumption of activities.

B12.2 If CB collection activity is discontinued at any fixed CB Collection Site for a period exceeding six (6) months, the CBB Director or designee shall review and renew the CB collection contract with that site.

Explanation:

This standard applies to fixed CB Collection Sites and CB Processing Facilities that are a part of a FACT-NetCord accredited CBB. It is not applicable to non-fixed CB Collection Sites that collect related or unrelated CB units. These collecting health care professionals must; however, demonstrate an understanding of their participation in acquiring a unit.

Interruption of operations are rare events and are often not foreseen in the distant future. However, the CBB must demonstrate the awareness of the potential for this to occur. At a minimum, the bank must reference responsibilities and procedures to follow in the event of an operation, such as a contingency plan.

STANDARD:

B12.3 If a CBB discontinues banking of new CB units:

B12.3.1 There shall be competent staff to oversee, maintain, and distribute the inventory.

B12.3.2 There shall be a process to continue the stability program.

Example(s):

Depending on the extent to which operations are interrupted, CBBs may consider contracting these services from a third party.

STANDARD:

- B12.3.3 There shall be a process to distribute CB unit contiguous segments and samples for testing, including pre-release testing.*
- B12.3.4 All records of the entire inventory in storage shall be maintained.*
- B12.3.5 The staff shall maintain communication with all relevant registries and Clinical Programs, if applicable.*
- B12.3.6 For related CBBs, the staff shall maintain communication with donor families, if applicable.*

Explanation:

This requirement is applicable only to time-sensitive communications related to activities that are still in operation.

STANDARD:

- B12.4 Prior to the reestablishment of either CB collection or banking, as applicable, the following at a minimum shall be documented:*
 - B12.4.1 Review of all procedures to confirm that methods are consistent with current practices.*
 - B12.4.2 Inspection of all reagents and supplies to confirm none will be used past its expiration date.*
 - B12.4.3 Validation, calibration, and maintenance of all equipment have been completed within the time periods specified in the Standard Operating Procedures and manufacturer's instructions.*

Explanation:

CBBs must verify that their processes, supplies and reagents, and equipment comply with current NetCord-FACT Standards prior to reestablishing operations.

STANDARD:

- B12.5 Cessation of operations.*
 - B12.5.1 The CBB shall follow all contractual obligations that are specified in written agreements with CB Collection Sites, donor families, registries, and other entities as applicable.*

Explanation:

Operations must be discontinued in a manner that provides for the safety of inventory in order to maintain CB unit potency. CBBs that receive inventory from CBBs that cease operations are expected to follow the Standards related to transfer of inventory (B10), records (B11), etc. For units already released, records should be transferred to another bank and the transplant physicians should be notified.

Evidence:

Contracts with donor families for related banks should describe what will happen in the event the CBB ceases all operation (see also B2.4 on written agreements).

Example(s):

There are many possible types of written agreements that a CBB would need to honor in the event it ceases operations, such as:

- Contracts with donor families (related CB units),
- Contracts with CB Collection Sites in relation to duration of the agreement, supplies and reagents, etc., and
- Contracts with registries (management of CB units already listed).

CORD BLOOD DONOR MANAGEMENT AND COLLECTION STANDARDS

PART C

- C1 General Requirements
- C2 Cord Blood Collection Personnel Requirements
- C3 Policies and Standard Operating Procedures
- C4 Informed Consent
- C5 Maternal and Infant Donor Evaluation
- C6 Cord Blood Collection
- C7 Transportation and Shipping of Unmanipulated Cord Blood Units Between the Cord Blood Collection Site and the Cord Blood Processing Facility

PART C: CORD BLOOD DONOR MANAGEMENT AND COLLECTION STANDARDS

C1: GENERAL REQUIREMENTS

STANDARD:

C1.1 These Standards shall apply to all CB activities.

Explanation:

CBBs have multiple relationships with CB Collection Sites and many approaches exist. No matter how the relationship between a CBB and CB Collection Site(s) is arranged, the Standards in Part C apply to all CB collections and donor management. This includes related and unrelated collections at both fixed and non-fixed collection sites.

The CBB applying for accreditation is responsible for ensuring that all aspects of donor management and collection, no matter where these activities take place, are in compliance with these Standards. Sites that accept ongoing responsibility beyond an individual collection, such as storage of supplies and reagents, may be inspected.

Evidence:

The CBB must be prepared to show the inspector contractual agreements for all sites and the organizational chart of the CBB with descriptions of the relationships, responsibilities, and roles of all facilities and personnel.

Example(s):

A CB Collection Site may be in a maternity unit in a hospital, a birthing clinic, or in a home environment. The collection service may be staffed entirely by employees of the CBB, by health care professionals of the maternity unit/birthing clinic, or a mix of both.

A CB Collection Site may use a combination of physicians, midwives, nurses, and CBB staff to perform some or all of the activities involved in recruitment, consent, collection, donor selection, and donor screening. Training records and competency monitoring must be available for all staff participating in the activities.

Figure 5: Cord Blood Collection Models outlines the various methods by which collection activities may be arranged. All of the scenarios in this table must meet these Standards.

Figure 5: Cord Blood Collection Models

Site	Contract/ Agreement with	Donation initiated by	Type of CB unit		Collection model			Reagents & Supplies provided by			Staffing of Site						Training methods provided by CBB				
			unrelated	related	in-utero	ex-utero	in-utero + ex-utero	hospital	CBB		Collection responsibility			Shipping responsibility			observation	hands-on	competency	presentation	
									individual supplies for collection activities	prepared collection kits	OB/midwife	hospital - phlebotomist/nurse/ research	CBB staff	OB/midwife	hospital staff - phlebotomist/nurse/ research	CBB staff					donor family
Fixed	Collection Site	CBB	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fixed	Donor mother	Donor mother or physician of intended recipient		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fixed	Physician or physician's group	Donor mother or physician	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-Fixed	Donor mother	Donor mother or physician of intended recipient	X	X	X	X	X		X	X	X	X	X	X	X						X
Non-Fixed	Physician's group	Physician's group	X	X	X	X	X	X	X	X	X	X	X	X	X						X

STANDARD:

C1.2 The CBB shall provide documentation to the CB Collection Site that outlines requirements for complying with CBB collection policies and Standard Operating Procedures.

Explanation:

Documentation must specify not only the requirements for the collection and related procedures, but also who is responsible for them.

A written agreement between a CBB and a CB Collection Site should specify the relationship between the two facilities. Such agreements include administrative aspects such as scope of responsibility and understanding of participation, and also technical aspects such as method of collection, temperature, and length of storage of supplies. There must also be evidence of CB Collection Site compliance with CBB policies and SOPs related to donor selection and screening, collection staff training, performance of collection, and transportation and shipment to the CBB.

For collections at non-fixed sites where the contract may only involve the CBB and family, there should be an obvious mechanism of education and expectations communicated to the collecting health care professional. In addition to policies, SOPs, and instructions for collection, banks must also engage parents by providing materials with clear instructions and responsibilities. (Multiple gestational births do not require multiple agreements.)

Even though responsibilities for CB collection, labeling, and transport or shipping at non-fixed sites are given to the donor's family and the collecting health care professional, the CBB is obligated to document that the CB Collection Site and all responsible parties follow the CBB policies and procedures related to the collection of CB. See B3 and C3 for a list of all required policies and SOPs required for CB collection.

Evidence:

Inspectors will review agreements for inclusion of appropriate procedures and responsibilities that are required. The documentation should include clear descriptions of roles and responsibilities and training requirements.

Documentation of responsibilities will usually be at the CBB rather than at the CB Collection Sites. The inspection team will need to coordinate responsibilities for reviewing these responsibilities.

Example(s):

Written agreements for CB donor management and collection at fixed CB Collection Sites are usually between the CBB and the fixed site. The agreement for related donations is typically between the CBB and the family, not with the CB Collection Site.

For unrelated donations at non-fixed sites, the agreement may be between the health care professional and the CBB or between the donor mother and the CBB. Generally, the infant donor's mother initiates the process for collection of unrelated CB units at non-fixed sites and works with the health care professional to confirm he/she meets elements in the written agreement. If this is the case, the CBB should include this in the instructions sent to the infant donor's mother.

Typically, the donor family is responsible for enrollment, providing medical history, and transport or shipping. Health care providers must be responsible for training and performing the CB collection procedure in accordance with the CBB policies and procedures.

Written agreements and informed consent documents can be organized in many ways as long as all of the required elements are included; for example, collections at non-fixed sites may include the written agreement and informed consent in a single document.

STANDARD:

C1.3 The CB Collection Sites shall have processes to prevent the introduction, transmission, or spread of communicable disease.

Evidence:

Sites that are subject to inspection should provide evidence of:

- Policies and procedures for cleaning and sanitation,
- Personnel screening and use of personal protective equipment,
- Segregation of supplies from one collection to another,
- One cord blood collection performed at a time,
- Records of cleaning and sanitation,
- Tour of site and demonstration of procedures. Documentation at the CBB should demonstrate adequate instructions and SOPs for collection personnel concerning the prevention of communicable disease transmission.

Example(s):

CBBs in the U.S. that collect CB units for unrelated allogeneic use must follow GMPs as a requirement for FDA licensure.

STANDARD:

C1.4 There shall be adequate space for the performance of the collection procedure.

Explanation:

The space used for collection of CB should be well defined and adequate. If other activities are performed using the equipment and in the space assigned at the CB Collection Site, concurrent activities must be performed in such a way as to not pose a risk of contamination or CB unit mix-up and must not adversely affect the integrity of the collected cells.

Example(s):

The collection procedure may be performed on a cart, in the home with ample room for the supplies and the collector, etc.

STANDARD:

C1.5 There shall be secure storage of the CB unit, associated samples, maternal samples, and documents until they are transported or shipped to the CB Processing Facility.

Explanation:

A secure environment is one where the general public or unauthorized persons do not have access. There should be a designated area away from areas of public traffic. If not locked or demarcated by a wall or door, it should generally be attended. CB units must be kept safe and free from tampering; only authorized personnel should have access to them and their associated documentation. A chain of custody needs to be established and documented.

Evidence:

There must be evidence that opportunity for tampering with the collected CB unit and its components is reasonably minimized. This could be verified with direct observation, forms that trace the chain of custody of the unit, or through other means by which the CBB documented the security of the unit.

Example(s):

Secure storage may be achieved with separate rooms or via a secured shipping container.

STANDARD:

C1.6 There shall be a designated area for appropriate and secure storage and preparation of the equipment, supplies, and reagents needed for the collection procedures.

C1.6.1 Equipment, supplies, and reagents shall be stored according to the manufacturer's recommendations in an area and manner appropriate to protect their integrity and functionality.

C1.6.1.1 There shall be documentation of appropriate storage of all supplies, reagents, and CB units.

Explanation:

Many reagents and supplies have specified storage temperatures. CB units, associated samples, and maternal blood samples must be stored within defined environmental conditions to maintain their viability.

Evidence:

The inspector should look for environmental/temperature logs of storage areas for reagents and supplies, CB units, associated samples, and maternal blood samples.

Example(s):

One approach to complying with this standard would include recording the temperature of the collections kit or the area where kits are stored. This could be accomplished by:

- Appropriate documentation of temperature readings or min/max thermometers, or
- Use of data loggers.

STANDARD:

C1.6.2 Supplies and reagents shipped to CB Collection Sites from the CBB shall be in an outer container validated to maintain the designated temperature range.

C1.6.3 *Supplies and reagents shall be used prior to their expiration dates.*

Explanation:

This standard applies to equipment, supplies, and reagents, and to the shipment and storage of collection kits. Patient care areas are designed to maintain an environment that is comfortable for staff and patients and thus are kept within a limited temperature range, but the inventory of supplies and reagents must also be stored according to manufacturer's recommendations in a way that protects their integrity and function. Conditions such as temperature and humidity during storage at fixed collection sites and shipment to remote and non-fixed sites can affect the quality of the reagents and supplies and in turn the quality of the collected CB unit.

Evidence:

If storage issues may negatively affect the integrity or function of supplies and reagents, such as if the supply or reagent is stored in direct sunlight, on a window ledge, or on a shelf under or over an illuminated light fixture, this will be noted in the inspection report.

The CBB should make available to the inspector records of temperature and humidity in storage areas. Storage conditions and the manufacturer's recommendations should be in agreement.

Inspectors may also review information provided to donor mothers/physicians regarding storage of the kits before use.

Inspectors will review expiration dates on stored inventory and verify stock rotation. There should be documentation of inspection of supplies and reagents prior to use.

Example(s):

The following are methods that may be used to confirm the temperature of storage areas is appropriate for supplies and reagents:

- Temperature monitoring records for storage areas, with evidence of review of records and follow up of excursions outside of the documented acceptable ranges.
- Documentation that collection supplies were sent under validated conditions.

STANDARD:

C1.7 *The CB Collection Site shall have Standard Operating Procedures that utilize universal precautions and are designed to minimize risks to the health and safety of employees, volunteers, and visitors, including at least:*

C1.7.1 *Bloodborne pathogens.*

C1.7.2 *Hand washing and/or decontamination.*

C1.7.3 *Chemical hazards.*

C1.7.4 *Latex allergy.*

Example(s):

The CB collection sites shall utilize universal precautions published by the Center for Disease Control and the Occupational Safety and Health Administration in the US, or internationally relevant local equivalent.

STANDARD:

C1.8 Gloves and protective clothing shall be worn while handling biological specimens. Such protective clothing shall not be worn outside the work area.

C1.9 When a CB collection kit is prepared and sent from the CBB, adequate instructions and materials shall be provided.

C1.9.1 The CB collection kit shall be transported or shipped under conditions validated to maintain the designated temperature range from the time it leaves the CBB until it is received by the CB Collection Site or the donor's family.

C1.9.2 There shall be adequate instructions and materials to store the collection kit prior to collection.

C1.9.3 There shall be adequate instructions and materials to collect, label, store, pack, and transport or ship the CB unit, associated samples, and maternal samples to the CBB.

Explanation:

The validation of the conditions under which a CB collection kit is transported or shipped must account for extremes in temperature ranges given the variable conditions in which the kits may be exposed. Temperature should be monitored using a min/max thermometer or data logger.

For non-fixed sites, the donor mother must be provided instructions for how to store the collection kit prior to delivery of her baby.

Evidence:

The CBB must provide the inspector with the validation study for the shipping/transport container, and the instructions for receipt and storage of the collection kit provided to the maternal donor or CB Collection Site.

Example(s):

CB collection kits may be placed in unacceptable temperatures at any point in time, for example:

- Before delivery: A delivery truck may be delayed.
- Before collection: A mother who resides in a warm climate may incorrectly store the kit in her automobile,
- At the time of collection: A collector may place the kit next to a sunny window.

Temperature monitoring of the kit during distribution helps identify if the kit was potentially placed in an environment outside the acceptable storage temperature range for the reagents and supplies.

STANDARD:

C1.10 Identity of supplies and reagents including manufacturer, lot number, and expiration date shall be documented for each collection.

Explanation:

A variety of approaches are employed by CBBs for the acquisition and tracking of supplies and reagents. If collection supplies are furnished by the CB Collection Site, appropriate information, such as lot number, manufacturer, and expiration date, must be recorded and provided to the CBB. Any supplemental supplies added to a collection kit at the CB Collection Site should be documented. There should be a distinction between “critical supplies” and other type of supplies. The CBB should define what it specifically considers as “critical supplies.” At minimum, this includes the collection bag and its anticoagulants and needles.

Evidence:

There should be documentation that permits the tracking and tracing of supplies and reagents to the CB unit.

The inspector should be provided documentation that verifies the use of reagents and supplies prior to the expiration dates. Where kits are provided by the CBB to a CB Collection Site, there must be a process by which the collection site personnel can confirm that the reagents and supplies have not expired.

Example(s):

In some CBBs, the central facility controls the collection supply inventory, and assumes responsibility for recording lot numbers and expiration dates of components in the kit. This documentation is likely retained by the CBB and need not be kept at the CB Collection Site. Consideration should be given to recording lot numbers and expiry dates in such a manner as to facilitate a recall or investigation, as required.

C2: CORD BLOOD COLLECTION PERSONNEL REQUIREMENTS

STANDARD:

C2.1 All CB collection personnel shall comply with these Standards.

Explanation:

It is the responsibility of the CBB to provide or confirm that collection personnel have adequate training to perform CB collection procedures, and to have adequate numbers of trained personnel available for the collection of CB relative to the workload.

The number of staff available and responsibilities of the staff will vary from institution to institution and no specific numbers of staff members are required by these Standards.

It is understood that the contract in related banking programs is often between the family and CBB, not the CB Collection Site. However, this does not remove the obligation of the CBB to assure the training

and competency of the health care professional to achieve the highest quality collection for its customers.

Evidence:

The CBB, and also the inspection team, will make a judgment of the adequacy of the staff support. Insufficient staffing may be indicated by excessive overtime, rapid turnover of personnel, incomplete record keeping, or an increase in adverse events.

STANDARD:

C2.2 *All CB collection personnel shall have a defined line of communication with relevant CBB personnel.*

Explanation:

Where there are CB Collection Sites that are not staffed by CBB personnel, there shall be a designated individual who is responsible for communication with the CBB Collection Director or designee. At CB Collection Sites where individual health care professionals perform collections, the individual performing the collection may serve as the contact person.

STANDARD:

C2.3 *All collections shall be performed by health care professionals trained for the collection procedure.*

C2.3.1 *Training on the collection procedure shall cover each aspect of the CB collection process, and include at a minimum:*

C2.3.1.1 *The use of the collection supplies and reagents.*

C2.3.1.2 *Cleaning of the umbilical cord to minimize the risk of contamination with microbes or maternal blood.*

C2.3.1.3 *Use of the CB collection bag to avoid microbial contamination and clotting.*

C2.3.1.4 *Labeling.*

C2.3.1.5 *Verification of the identity of the donor.*

C2.3.1.6 *Safety of the maternal and infant donors.*

C2.3.2 *The collecting health care professional's training shall be documented.*

C2.4 *There shall be documented training on the following procedures for all relevant personnel:*

C2.4.1 *Packaging, storage, and shipping or transportation of the CB unit as applicable.*

C2.4.2 *If applicable, review of medical records and physical examination of the maternal and infant donors for risks of communicable diseases.*

Explanation:

Collection personnel, whether employed by the CBB or not, must have training in key tasks that they perform, and initial and ongoing competency and training must be documented.

In banking models that utilize collection kits for non-fixed CB Collection Sites, the collector often is not responsible for packing, storing, and shipping the CB unit. This task is usually the responsibility of the donor family; however, if the collector does in fact perform that function, he/she must be trained.

Evidence:

Documentation of training must include written acknowledgement from both the trainee and trainer. This could be via email, a training form, or a sign in list from a training session.

Example(s):

There are many approaches to collection methods and distribution of the responsibilities involved with collection. Activities may be solely performed by CBB personnel. Alternatively, maternal screening and eligibility may be performed by nursing personnel with the collection by a health care professional.

Training of collecting health care professionals can be accomplished by a variety of means, such as video or web-based presentations, with or without questions to assess knowledge gained from the training, followed by acknowledgement by the health care professional of his/her understanding of the principle elements of collection.

C3: POLICIES AND STANDARD OPERATING PROCEDURES

STANDARD:

C3.1 *The CBB shall establish and maintain policies and/or Standard Operating Procedures addressing critical aspects of collection operations and management in addition to those required in B2. These documents shall include all elements required by these Standards, be consistent with the policies and Standard Operating Procedures of the CBB, and address at a minimum:*

Explanation:

There must be collection policies, SOPs, or both that address critical aspects of cord blood collection. Donor management and collection processes must be consistent with the policies and SOPs required by the CBB in B3.

Evidence:

Examples of policies and SOPs that have been revised with appropriate signatures and documentation of training should be noted during the inspection; this is especially important in CBBs where the central facility manages separate CB Collection Sites.

Policies and SOPs relevant to CB collection are required to be available at all sites. Inspectors should observe how personnel perform procedures compared to written instructions.

Example(s):

There are several ways to organize policies and SOPs depending on the CBB's relationship with the CB Collection Site:

- All policies and SOPs are created by the CBB and used by the CB Collection Site,
- Some policies and SOPs are created by the CBB and some are created by the CB Collection Site, or
- All policies and SOPs are created by the CB Collection Site (fixed sites).

Most SOPs should be created by the CBB itself. However, some SOPs may be created by the individual CB Collection Sites as they may apply only for the site, such as facility cleaning and sanitation and hours of operation.

STANDARD:

C3.1.1 *Donor recruitment and education.*

C3.1.2 *Maternal and infant donor screening.*

Explanation:

CB Collection Sites are responsible for assessing the general health of the mother; CBBs must determine donor eligibility by reviewing medical and behavioral history and physical examination results. The collection sites must have a process to review results of the physical examination, but banks may differ on the timing of when the medical and behavioral history is obtained. SOPs regarding maternal and infant donor screening and eligibility criteria are required of the CBB; however, they often are applied after the CB unit has arrived at the CB Processing Facility. SOPs must outline who collects the information and when, and detail what the screening includes. The CBB must have SOPs regarding how the results are interpreted and what results are acceptable, even though that process is performed after the CB unit arrives at the bank. The CBB is not responsible for performing the physical examination, but may obtain the results from the health care provider or institution.

Example(s):

CBBs may have policies for automatic deferral of donors before the collection is performed, or all donor eligibility determination may be made after the CB unit arrives to the CB Processing Facility (but before the unit is available for search).

STANDARD:

C3.1.3 *Informed consent.*

C3.1.4 *Suitability assessment of maternal and infant donor.*

Explanation:

Safety of the donors is paramount, and collection practices must not jeopardize the health and safety of either the maternal or infant donor.

STANDARD:

C3.1.5 *Interaction between the CB Collection Site and the CBB.*

C3.1.6 *Documentation of infant donor health at birth.*

Example(s):

Infant birth data may be obtained via the clinical notes of the physical examination. Copies of the medical record are not required, but trained staff could extract the salient points that have bearing on the safety of the unit.

STANDARD:

C3.1.7 *Maintenance of linkage of the CB unit to the maternal and infant donor.*

C3.1.8 *Collection of CB, associated samples, and maternal samples.*

Explanation:

Most CBBs create samples from aliquots of the CB unit upon arrival at the CB Processing Facility; however, some CB Collection Sites may collect samples from the CB unit, umbilical cord, or placenta at the time of delivery. These Standards were written to include associated samples for these situations.

STANDARD:

C3.1.9 *Completion of records at the CB Collection Site.*

C3.1.10 *Labeling of the CB unit, associated samples, maternal samples, and documentation.*

C3.1.11 *Process control, including product specifications and nonconforming products and processes.*

C3.1.12 *Storage and packaging of CB units, associated samples, maternal samples, and documentation at the CB Collection Site.*

C3.1.13 *Transport and shipping of the CB unit, associated samples, maternal samples, and completed records to the CB Processing Facility.*

C3.1.14 *Acceptable levels of hemodilution of maternal samples used for communicable disease testing.*

C3.1.15 *Personnel and collector training and continued competency for the procedures performed.*

C3.1.16 *Electronic record entry, verification, and revision, if applicable.*

C3.1.17 *CB unit records.*

C3.1.18 *CB unit disposition.*

- C3.1.19 *Equipment monitoring, qualification, and maintenance.*
- C3.1.20 *Facility and environmental management.*
- C3.1.21 *Materials management.*
- C3.1.22 *Cleaning and sanitation procedures.*
- C3.1.23 *Disposal of medical and biohazardous waste.*

Evidence:

Procedures for disposition of biohazard waste should be available to the inspector. If this task is contracted with an external company, minimal qualifications for the company and also the contract should be available during the inspection.

STANDARD:

- C3.1.24 *Hygiene and use of personal protective attire and equipment.*
- C3.1.25 *Emergency and safety procedures.*
- C3.1.26 *Biological, chemical, and, if applicable, radiation safety.*
- C3.1.27 *Disaster plan.*

Explanation:

The disaster plan may include the larger institution's disaster plan, but the CBB must address specifically the needs of the CBB.

Example(s):

The disaster plan may include key CBB personnel that must be contacted, a flow chart for maintaining operations (if possible), etc.

STANDARD:

- C3.1.28 *Disposal of a CB unit.*

C4: INFORMED CONSENT

STANDARD:

- C4.1 *Informed consent from the mother or an agreement between the mother and the CBB shall be obtained and/or verified and documented by a trained individual in accordance with Applicable Law.*

Explanation:

These Standards are minimum requirements and require a trained individual to obtain the informed consent. Some local laws and regulations, such as some states in the U.S., require physicians or licensed health care professionals to obtain the consent.

Example(s):

Some CBBs may obtain informed consent via a form that is completed by the mother and mailed to the CBB. A trained individual must verify that the consent was properly obtained prior to collection.

In some instances, persons other than the mother are required to provide consent. This must be reflected in the consent process, when applicable.

STANDARD:

C4.1.1 Informed consent or an agreement between the mother and the CBB shall be obtained and documented while the mother is able to concentrate on the information and is not distracted by aspects of labor.

Explanation:

Most women present to the hospital for induction or in early stages of labor, allowing time for the informed consenting procedure. The potential donor must be alert, comfortable, and able to give informed consent and must not be distracted by pain or other labor activities. General or systemic anesthesia and sedation medications (such as benzodiazepine or similar) must not have been administered prior to the consent process; however, an epidural is acceptable. The collection staff must determine the appropriate time to obtain the informed consent (information can be obtained by consulting with the mother's nurse).

Informed consent processes vary among CBBs. The Institute of Medicine publication, *Cord Blood, Establishing a National "Hematopoietic Stem Cell Bank Program,"* reports on the importance of obtaining informed consent for the donation of any CB unit, regardless of the timing of collection or its potential use. The report recognizes the practicality and demographic realities of the donor communities while emphasizing that informed consent procedures must be designed to protect the interests of the infant donor's family and educate the infant donor's mother about the various options for CB use. (Refer to pages 107-112 of the report.)

Example(s):

The United Kingdom Human Tissue Authority (HTA) published a Code of Practice on Consent in September 2009. This document can be found online at https://www.hta.gov.uk/sites/default/files/Code_of_practice_1_-_Consent.pdf.

The United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA) also allows documenting informed consent with recordings of the discussion.

STANDARD:

C4.1.2 In cases of a surrogate mother, informed consent or an agreement shall be obtained and documented from both the surrogate mother and the genetic mother.

C4.2 *All aspects of participation in CB donation shall be discussed with the mother in a language and with terms that she understands.*

Explanation:

A person who provides interpretation or translation must understand the collection, storage, and banking procedures, as applicable, sufficiently enough to explain the process adequately to the mother. The explanation of the procedures must be understood by non-medical persons. If possible, the informed consent should be translated into the mother's native language.

Evidence:

The CB Collection Site should provide the inspector copies of consent forms in other languages or evidence of bilingual staff or a translation service.

Example(s):

A mother who does not speak the working language of the CB Collection Site should have materials available in her language or a language she understands. Alternatively, the materials may be interpreted through bilingual staff or a hospital interpreter and the activity documented. IRBs may require certain languages to be used routinely based upon the characteristics of the donor population.

STANDARD:

C4.3 *The CBB shall only perform steps in the CB banking process for which it has informed consent or a signed agreement from the mother, including at a minimum:*

C4.3.1 *Collection.*

C4.3.2 *Processing.*

C4.3.3 *Testing.*

C4.3.4 *Long-term storage.*

Explanation:

CBBs obtain and document informed consent in differing ways. These Standards do not prescribe how or when a CBB may obtain consent for various steps in the CB collection and banking process; however, only those steps to which the mother has consented can be performed.

The information that must be included in the consent process is listed in C4.5 through C4.7. It is the responsibility of the CBB to ensure that the relevant information is provided to the mother at the appropriate time during the CBB's informed consent procedure.

Example(s):

Many acceptable strategies can be applied to obtaining consent, especially in regards to the timing of consent for certain processes. Examples of different ways to comply include:

- Two-step process: pre-consent for collection followed by a full consent for obtaining health information and placing the CB unit into storage upon collection of an adequate unit. In this process, the pre-consent must include what steps will be taken by the CBB before the full consent is obtained. The CBB must obtain full consent before the unit is placed into long-term storage. This process may be used when a mother presents to a fixed CB Collection Site while in active labor.
- Single-step consenting process: full consent administered prior to collection to permit all aspects of collection and banking. This process may often be easier because it is less dependent on the nature of the delivery (e.g., duration of time from admission to the hospital to the delivery or administration of medication). This may be used for cases in which the donation process is initiated early in the pregnancy.

If the informed consent or agreement is obtained by mail, this may be an opportunity for the CBB to record the maternal donor's contact information (e.g., email or phone number) and provide answers to frequently asked questions.

STANDARD:

C4.4 The mother shall have an opportunity to ask questions.

Explanation:

The willingness to donate CB must be an individual choice of the mother. She must have the opportunity to ask questions that clarify the process of collection and donation and be free to withdraw at any time.

STANDARD:

C4.5 The informed consent or agreement between the mother and the CBB shall include the following information at a minimum for unrelated and related donations:

C4.5.1 The overall purpose and participation of the maternal and infant donors.

C4.5.2 An explanation of the collection procedure and activities in terms the mother can understand.

C4.5.3 The possible risks and benefits to the maternal or infant donor.

Example(s):

Risks include breach of confidentiality, receipt of unfortunate testing results, needle sticks, etc.

STANDARD:

C4.5.4 The possible alternatives to participation.

C4.5.5 The intent of the donation for either unrelated use or for related use.

C4.5.6 The mother will be asked to provide personal and family medical history.

- C4.5.7 *Personnel will be permitted to review the medical records of the maternal and infant donors.*
- C4.5.8 *Samples from the maternal and/or infant donors will be collected for communicable disease and genetic disease testing, HLA typing, and other testing, as applicable.*
- C4.5.9 *Maternal and CB unit samples will be stored for future testing.*
- C4.5.10 *The CBB will indefinitely maintain linkage between the maternal and infant donors and the CB unit.*

Explanation:

Samples for testing will be collected from the mother, the infant, or both. CBB will have procedures to notify the maternal donor, her physician, or both if any abnormal results are obtained.

Indefinitely means that no fixed time limit has been specified; i.e., the maintenance of linkage will continue for an unknown amount of time.

STANDARD:

- C4.5.10.1 *The CBB will notify the mother or her responsible physician, and governmental agencies when required, of positive or indeterminate communicable disease or genetic test results.*
- C4.5.10.2 *The CBB retains the right to follow up with the mother or relevant healthcare provider at a future date.*

Explanation:

The informed consent should make clear the possibility that the CBB could contact the infant donor's mother or relevant healthcare provider (e.g., the mother's physician, the infant donor's physician, etc.) at any time for follow up, and may be required to report test results in accordance with Applicable Law. This may include providing the infant donor's family information on CB unit test results (e.g., genetic disorder test results), or later when the CBB performs bank-initiated donor follow-up.

At some CBBs, it is the policy to contact the infant donor's family to update infant donor health screening prior to release of the CB unit for transplant.

STANDARD:

- C4.5.10.3 *Personal information related to the infant donor and the infant donor's family shall remain confidential and is only available for review by individuals designated by the CBB or as required by Applicable Law.*

Explanation:

In addition to health care professionals on a need-to-know basis to the extent allowed by Applicable Law, individuals designated by the CBB to review confidential information include accrediting agencies, external auditors, and other individuals the CBB may request to review the information for quality purposes.

STANDARD:

- C4.5.11 *The CB unit will be processed, stored, and made available for use.*
- C4.5.12 *The CBB's policies for disposal of CB units, including at a minimum:*
 - C4.5.12.1 *Nonconforming CB units.*
 - C4.5.12.2 *Related CB units, if these units are no longer required.*
 - C4.5.12.3 *Agreed-upon duration of storage for related CB units.*

Example(s):

There are many reasons why a CBB may choose to discard nonconforming CB units, such as those with cell counts or microbial contamination results that do not meet the bank's criteria, positive infectious disease markers, etc.

STANDARD:

- C4.6 *Informed consent for unrelated donation shall also include:*
 - C4.6.1 *The right of the mother to refuse without prejudice.*
 - C4.6.2 *If the CB unit is listed for unrelated use, the infant donor and the infant donor's family no longer have ownership of the CB unit, the CB unit is a donation that will be made available to other individuals, and the CB unit will not necessarily be available to the infant donor or the infant donor's family at a later date.*
 - C4.6.3 *If the CB unit is listed for unrelated use, information regarding the CB unit, including donor eligibility, will be shared with registries nationally and/or internationally as applicable, and with other individuals as appropriate.*
 - C4.6.4 *If the CB unit may potentially be used for reasons other than the primary intent, including for purposes other than clinical administration, this shall be fully disclosed in the informed consent or agreement between the mother and CBB.*

Explanation:

In jurisdictions that permit the practice, some CBBs utilize a model in which CB units originally collected for related use are subsequently released for unrelated transplantation. This model has considerable implications for informed consent. The maternal donor must be informed about the practice and the conditions under which the CBB may wish to release the CB unit for unrelated administration.

If a CBB utilizes this model, the CBB must ensure the unit meets all applicable requirements for unrelated CB units (including donor eligibility), even if it was originally collected for related use.

Example(s):

The CB unit may be collected for related use, but then listed for unrelated use if the family no longer wishes to store the unit for its own use. Alternatively, a unit may be collected for unrelated use, but testing shows insufficient volume and the unit is used for research instead.

The U.S. FDA regulations do not currently provide a mechanism for crossing over products intended for related use to use by an unrelated recipient.

Examples of possible uses of CB units other than clinical use include research, quality control, validation studies, and stability studies.

STANDARD:

C4.7 *If the CB unit is intended for related use, the mother shall also be informed that the release of the CB unit will be limited to the donor family, intended recipient(s), or the infant donor.*

C4.7.1 *If the CB unit is intended for related use but may potentially be used for unrelated use, the mother shall be informed of the process for making the CB unit available for unrelated use.*

C4.8 *If the intended use of the CB unit is unknown, donor eligibility shall be determined.*

C5: MATERNAL AND INFANT DONOR EVALUATION

STANDARD:

C5.1 *There shall be written criteria for maternal and infant donor evaluation and management.*

C5.1.1 *There shall be a process for maternal and infant donor identification and linkage.*

C5.1.2 *There shall be criteria and evaluation procedures in place to protect the safety and confidentiality of the infant donor and mother.*

C5.1.3 *If a related CB unit may potentially be used for unrelated donation, the evaluation process shall include all evaluation requirements for unrelated CB units at the time of collection.*

C5.1.4 *There shall be a policy for follow-up of donors for management of donation-associated adverse events.*

Explanation:

This standard requires that the CBB has in place written SOPs defining all aspects of maternal and infant donor identification, evaluation, selection, and management. This standard is intended to promote the safety of the maternal and infant donor. While it is recognized that adverse events are highly unlikely for *ex utero* collections, all maternal and infant donors shall be evaluated for donation-associated adverse events (for example, needle stick injuries).

The standard does not define an acceptable donor. Instead, it requires that the CBB define specifications for CB unit banking. It also requires that each aspect of this process be performed according to written SOPs and the results of the evaluation be documented.

Evidence:

Policies and SOPs for donor selection must be written, clearly defined, and unambiguous. Compliance with these SOPs may be verified by reviewing a specific donor evaluation.

STANDARD:

C5.1.5 *Maternal and infant donor evaluation results shall be documented.*

C5.1.6 *Any abnormal result relevant to the health of the maternal or infant donor shall be reported to the relevant healthcare provider, maternal donor, and governmental authority according to Applicable Law.*

Explanation:

Even if a CB unit is not collected, abnormal results must be reported to the maternal donor or her physician so that the appropriate follow-up may take place.

STANDARD:

C5.2 *Maternal and infant donor screening shall include a medical history, review of medical records, and review of physical examination findings.*

Explanation:

The questions included in the medical and genetic history interview will vary based on the population and culture of the geographical region and Applicable Law. Screening must include issues of high-risk behavior that may put the maternal donor at risk for infectious diseases that may transmit to the CB unit recipient.

Example(s):

Methods to collect medical and genetic history include in-person discussions, forms with follow-up by the CBB, telephone interviews, etc.

FDA published the guidance, "Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products," to provide recommendations for screening donors of HCT/Ps for risk of transmitting the Zika virus. FDA now considers the virus a relevant communicable disease or disease agent (RCDAD) as defined in 21 CFR 1271.3(r)(2). Therefore, review of relevant medical records must indicate that a potential donor of

HCT/Ps is free from risk factors for, or clinical evidence of, Zika virus infection for the purpose of determining donor eligibility. Newer guidance may be issued, and other countries may have additional guidelines. This document can be found at:

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM488582.pdf>

STANDARD:

C5.2.1 *History shall be obtained and documented while the mother is able to concentrate on the information and is not distracted by aspects of labor.*

C5.2.2 *The history shall be obtained in a language the mother understands.*

C5.2.2.1 *If an interpreter or translator is utilized, the identity of the interpreter or translator shall be documented.*

C5.2.2.2 *Family members shall not serve as interpreters or translators.*

Explanation:

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

STANDARD:

C5.2.3 *The mother and surrogate mother, if applicable, shall affirm that all the information provided is accurate to the best of her knowledge.*

C5.2.4 *The mother shall be provided with information to contact the CBB if the infant donor later develops a serious disease.*

Example(s):

There are a variety of ways this can be accomplished: through a contact card, on a copy of consent forms, or in a brochure given to the mother at donation, which may list examples of serious disorders that would prompt notification.

STANDARD:

C5.3 *A medical and genetic history of the infant donor's family shall be obtained from the genetic mother.*

C5.3.1 *The history shall at a minimum request information regarding the infant donor's first-degree relatives and, when applicable, egg, sperm, or embryo donors.*

Explanation:

The CBB must make an attempt to elicit the medical and genetic history from all first-degree genetic relatives, including egg, sperm, or embryo donors. In some cases, the mother may not know the history of all relatives. This must be noted for further review by the CBB Medical Director, who will determine if the CB unit may or may not be stored.

STANDARD:

C5.3.2 *The history shall include at a minimum genetic history, malignant disease, and inherited disorders that may be transmissible to the recipient.*

Explanation:

Genetic history refers to any hematopoietic or metabolic disease present in the family and may be passed along to the recipient. History from first-degree relatives is most likely to elicit relevant information. Sometimes a donor will not be able to provide information about a relative, but the bank should make a good faith effort to obtain this information.

Example(s):

Genetic history should include questions screening for metabolic disorders such as Tay Sachs (for the purpose of avoiding transplant of CB from an affected donor in the setting of treatment for that specific disease) or disorders of the blood and immune system (e.g., sickle cell disease, thalassemia, and immunodeficiency syndromes).

Medical history will elicit information such as leukemia and other cancers or auto-immune diseases in first-degree relatives.

The CBB must attempt to elicit information regarding all of the parties named in this standard but it does not necessitate exclusion of the CB unit if history cannot be obtained, for instance, from a deceased grandparent, absent father, or adopted parents. In these cases, the CBB should inform the Clinical Program.

STANDARD:

C5.4 *A history for the mother's communicable disease risk behavior shall be obtained.*

C5.4.1 *The mother's communicable disease risk behavior shall be obtained in a confidential manner.*

C5.4.2 *The history shall include the mother's prenatal communicable disease testing, if known, and results of other general medical testing that could indicate a risk of communicable disease transmission.*

Explanation:

The rationale for requiring infectious disease and high-risk behavior history on the birth mother is driven by the fact that the woman carrying the infant shares circulation and, consequently, blood and body fluids through which infectious agents may be transmitted. History of potentially blood transmissible diseases must be obtained from the mother, tracked with the CB unit, and released to the Clinical Program.

STANDARD:

- C5.4.3 *If history for communicable disease risk was obtained in advance of the maternal donor's presentation for delivery, the history shall be updated to include information up to the time of delivery.*

Explanation:

This standard applies to CBBs that educate and screen donors prior to delivery to determine eligibility for participation. Upon delivery or soon thereafter, information previously provided during screening must be verified, including any changes to infectious risk history that may have occurred since the time of completion of the initial screening process. In addition to the health questionnaire, any other types of illness or conditions at the time of delivery, such as fever, that may impact the quality of the CB unit needs to be included in the history.

Example(s):

Per FDA CFR Part 1271.3(s), relevant medical records are defined as a collection of documents that includes a current donor medical history interview, a current report of physical examination, and other medical records. The regulations do not specify the timing of the physical exam or donor medical history interview. It would be the establishment's responsibility to determine what constitutes as "current" and define it in their Standard Operating Procedures as described in §1271.47. To appropriately assess donors for the risks of infectious diseases, establishments should consider that some conditions or risks may be related to current state of the donor or a specified time frame by referring to Applicable Laws.

Some CBBs may have a policy to perform follow-up calls to maximize capture of local risk factors; for example, demonstration of disease with lengthy incubation periods in areas where WNV, SARS, or malaria is prevalent. CBBs find that information obtained through this activity relates to manifestation of genetic diseases in the infant not immediately detected at birth.

STANDARD:

- C5.4.4 *In the case of a surrogate mother who gives birth to an infant donor not genetically hers, a communicable disease risk history of the surrogate mother shall be obtained.*
- C5.4.5 *Travel history of the mother and surrogate mother, if applicable, shall be obtained. Travel-related donor eligibility shall be determined according to Applicable Law.*

Explanation:

CBBs should be familiar with applicable national disease center publications, including websites, for current travel restrictions and agents associated with travel. Travel restrictions do not necessarily exclude donors but may require special labeling and release documentation in accordance with applicable law.

HIV and hepatitis B transmission through high-risk behavior, such as intravenous drug use, incarceration, and prostitution, are well documented. CBBs must determine the necessity of including such CB units into the inventory and appropriately label and document the CB unit as ineligible, regardless of infectious disease testing results.

HIV-1 Group O is a communicable disease threat to inhabitants of certain African countries. Currently, not all test kits include tests that detect HIV-1 Group O. Travel history is important when using these kits.

Example(s):

Eligibility determination based on travel history is expected to change over time, and to vary among regions of the world. As regulations change, units already in inventory may be retained in quarantined storage if potential users are informed and units are appropriately labeled.

STANDARD:

C5.4.6 *In the case of sperm, egg, or embryo donation from a bank not licensed in accordance with Applicable Law, the communicable disease risk history of the sperm, egg, or embryo donor shall be obtained and reviewed.*

Explanation:

Because the medical and genetic history of egg and sperm donors impacts the risks of a CB unit, it is recommended that CBBs only accept into inventory units for which the donors' medical and genetic history has been collected. In most cases, this history would be obtained by the egg or sperm bank, and the actual documentation does not need to be at the CBB if the egg or sperm bank is licensed by the relevant regulatory agency.

If no genetic history is available for these donors, it is recommended that unrelated allogeneic donation be deferred to eliminate risk of transferring genetic or inherited disorders.

STANDARD:

C5.4.7 *There shall be screening for human transmissible spongiform encephalopathy, including Creutzfeldt-Jakob disease.*

Explanation:

CBBs are not required to test for Creutzfeldt-Jakob disease, but must ask questions to obtain information regarding any history of this disease.

STANDARD:

C5.5 *Infant Donor Screening and Testing.*

C5.5.1 *History of the current pregnancy and delivery shall be obtained and reviewed.*

C5.5.2 *The infant donor's birth data shall be obtained and documented, including gender, gestational age, other results of clinical examination, and if the infant is free of any finding suggestive of disease potentially transmissible through administration of a CB unit.*

Explanation:

Clinical examination of the infant donor is performed to evaluate risk of genetic disease transmission and also observation of any infectious process at the time of birth. This examination must be conducted by a licensed health care professional who would normally perform infant assessment after birth and may include, for example, evaluation for the following:

- Extra digits
- Absent thumb or radius
- Other congenital defects.

If an infant donor is delivered at term, documentation does not need to list the actual gestational age; however, pre-term deliveries must include the gestational age for further review by the CBB in accordance with its policies and procedures.

Example(s):

CBBs may either document the actual gestational age or indicate that the gestational age was greater than or equal to 34 weeks, which is required by these Standards. In some countries this requirement may be fulfilled at a later follow-up with the donor.

STANDARD:

C5.6 *Maternal Samples.*

C5.6.1 *Blood from the birth mother shall be obtained within seven (7) days before or after collection of the CB unit for communicable disease testing required in D10.1.*

Explanation:

Obtaining samples within seven days of CB collection is necessary because the samples and their test results serve as surrogates for the CB unit, and testing should reflect the health of the mother at the time the unit is collected. This timeframe also limits the risk of failure to follow up with the mother and the scope for mix-up of samples. SOPs should define when samples should be obtained.

Evidence:

A procedure shall exist that explains in detail how and when maternal samples are collected, stored, and documented. The records of a CB collection should demonstrate compliance with this procedure.

STANDARD:

C5.6.2 *A sufficient volume of blood from the birth mother shall be obtained to meet the requirements in D4.3.1.*

C5.6.3 *Hemodilution of the birth mother prior to collection of maternal samples shall be assessed. The maternal sample acceptance criteria shall be defined.*

C5.6.4 *A sufficient volume of blood from the genetic mother should be obtained to meet D4.3.2.*

Explanation:

Standard D4.3.1 requires CB Processing Facilities to store a minimum total volume of 3.6 mL of serum and/or plasma from non-heparinized samples from the birth mother. Standard D4.3.2 requires suitable material from the genetic mother for preparation of at least 50 µg of genomic DNA.

The U.S. FDA guidance document, titled “Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps),” describes algorithms for determining if plasma dilution is sufficient enough to affect test results. This guidance is available at <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm091345.pdf>

Example(s):

For example, the guidance states that for donors over 12 years of age, more than 2000 milliliters of crystalloids within one hour immediately preceding the collection of samples is believed to be sufficient to affect the results of communicable disease agent testing. Based on this information, a CBB should specify in SOPs that samples should not be drawn if the maternal donor has received two or more liters of intravenous fluids in the previous hour.

C6: CORD BLOOD COLLECTION

STANDARD:

- C6.1 *CB collection practices shall protect the maternal and infant donor and have no impact on obstetric practice or patient care.*
- C6.1.1 *Delivery practices shall not be modified in an attempt to increase CB unit volume.*
- C6.2 *When in utero CB collection is performed, there shall be additional safeguards in place to protect the safety of the mother and the infant donor.*
- C6.2.1 *In utero CB collections should only be performed from documented singleton deliveries.*
- C6.2.1.1 *If CB collection is performed in utero in a multiple gestation pregnancy, all infants shall be delivered before any CB collection begins.*
- C6.2.2 *In utero CB collections for unrelated donations shall only occur in uncomplicated deliveries as determined by the licensed health care professional responsible for the delivery.*
- C6.2.3 *CB units collected in utero at less than 34 weeks’ gestation shall be based on an evaluation of infant donor safety by the licensed health care professional responsible for the delivery.*

Explanation:

CBB policy and practice must address the safety of mother and infant(s). There are risks unique to *in utero* collections that must be appreciated. It is expected that CB collection would not occur if there is any difficulty during delivery (e.g., excessive maternal bleeding, difficult delivery, fetal/newborn distress, or other serious maternal medical problem). Cord blood can be collected after multiple-birth deliveries; however, multiple deliveries may be more complicated; and there is a risk of misidentifying the CB units.

There are also situations of an unexpected twin who may have a shared placenta with the first delivered infant. In these settings, *in utero* collection of CB could have a disastrous impact on the undelivered twin. Thus *in utero* collections are recommended only from singleton deliveries. If the health care professional chooses to perform *in utero* collections in a multiple delivery then all babies must be delivered before the CB collection begins.

The standard requiring *in utero* CB collections after minimally 34 weeks gestation is based on the increased risk of a complicated delivery prior to 34 weeks, and the likelihood that the volume of collected blood would be low and not suitable for clinical use. However, *in utero* collection is allowed at the discretion of the licensed health care professional responsible for the delivery and CB unit collection, who must prioritize the safety of the mother and infant.

Evidence:

Compliance with this standard may be verified using documentation from the collection and delivery.

Example(s):

Complicated delivery includes but is not limited to:

- Multiple births,
- Active sexually transmitted disease at the time of delivery,
- Blood transfusion during labor and delivery,
- Maternal temperature greater than 102°F or 38.9°C,
- Malodorous placenta,
- Excessive maternal bleeding,
- Expulsion of placenta before or during collection.

STANDARD:

C6.3 *CB collection shall be performed according to written policies and Standard Operating Procedures.*

C6.3.1 *The identity of the maternal donor shall be verified.*

C6.3.2 *The identity of the cord blood collector shall be documented.*

C6.3.3 *CB collection procedures shall be validated to result in acceptable progenitor cell viability, cell recovery, and rate of microbial contamination.*

Explanation:

There are many acceptable approaches and elements in validating CB collection processes. They must all show that the process is validated by establishing by objective evidence that the process consistently produces CB units with endpoints in a defined range, such as collected CB volume, nucleated cell counts, progenitor cells, cell viability, and microbial contamination.

Evidence:

Current versions of approved policies and procedures must be available to collecting personnel at the CB Collection Site.

If it is not possible to observe an actual collection, the collection personnel should provide a verbal description, and must be prepared to demonstrate a mock collection procedure. The inspector can use this evidence to confirm that personnel follow the procedure and that the procedure meets the Standards.

Aseptic techniques should be employed to the extent possible during a collection or mock collection. Microbial contamination rates should be trended by collector, CB Collection Site, or other categories as appropriate to the CBB, and corrective actions taken when necessary. Records of validation of the collection procedure are usually inspected at the CBB where the quality activities are coordinated, performed, and analyzed, rather than at the individual CB Collection Sites.

STANDARD:

C6.3.4 Methods for CB collection shall employ aseptic techniques.

Explanation:

Aseptic technique as used in this Standard means those practices designed to reduce the risk of microbial contamination of products, reagents, specimens, patients, or donors. Techniques include control of environment, equipment, personnel, and practices in a manner that precludes microbiological contamination of the exposed product.

STANDARD:

C6.3.5 The CB collection bag shall be approved for use with human blood and sealed to prevent leakage and minimize the risk of cell loss and of microbial contamination.

Evidence:

Examples of ways to close the system at the Collection Site include the use of two clips, a clip and a knot, or two knots. Two seals may be used, but are not required by these Standards if the CBB can demonstrate that its procedure for sealing the bag is effective.

Example(s):

Examples of ways to close the system include the use of two clips, a clip and a knot, or two knots. Two seals are not required by the Standards if the CBB can demonstrate that its policy for sealing the bag is effective.

STANDARD:

C6.3.6 *All supplies and reagents for CB collection that come into contact with the CB unit shall be sterile.*

C6.4 *There shall be a unique numeric or alphanumeric identifier for the CB unit, associated samples, maternal samples, and associated documents.*

Explanation:

Unique refers to an identifier that is exclusive and distinctive and is not used for any other purpose. The essential point is that each CB donation, associated samples, maternal samples, and associated documents can be unambiguously traced from donor to recipient, through all distribution and processing steps, and at all storage locations.

Evidence:

A review of identifiers used to track multiple steps should verify that a unique identifier is used and adequately links the CB unit, samples, and documents throughout the entire process.

Example(s):

At collection, the identifier may be a combination of the infant donor mother's first and last name, medical record number, or the infant's birth date. To be unique, this requires at least two such identifiers in a combination unique in the environment of the CB Collection Site. If temporarily used, these identifiers should not be observable by the courier or general public. Once received in the CB Processing Facility, this information can be associated with and linked to a unique CB unit identifier that is assigned by the CBB.

STANDARD:

C6.5 *There shall be a written policy at the CB Collection Site for labeling of the CB unit, associated samples, maternal samples, and associated documents that permits tracking and tracing among the CB unit, infant donor, maternal donor, samples, and documentation.*

C6.6 *At completion of CB collection, the primary collection bag shall have affixed or attached, or be accompanied by, the information required in the Cord Blood Unit Labeling table in Appendix II.*

C6.7 *There shall be a written policy for storage of CB units, associated samples, maternal samples, and documents at the CB Collection Site prior to transport or shipping to the CB Processing Facility.*

C6.7.1 *CB units, associated samples, and maternal samples shall be maintained in a secure environment in a defined temperature range.*

Explanation:

A secure environment is one where the general public or unauthorized persons do not have access, and where opportunity for tampering with the collection and its components is reasonably minimized.

It is the CBB's responsibility to review the required specifications for storage of supplies and reagents that typically come from the manufacturer.

Evidence:

The labeling process must allow for proper identification and linkage among the mother, the CB unit, samples, and documents.

Example(s):

The CBB must have a process for assigning the correct maternal blood samples to the CB unit. There are many approaches to ensuring accuracy. One method is to have two individuals verify the labeling and link between samples and the unit.

STANDARD:

C6.7.2 CB units shall be maintained in a temperature range validated to protect cell viability.

Explanation:

Many studies have been published to demonstrate the duration and effects of room temperature (20-24°C) storage on liquid CB collections. Whatever storage temperature is used, it must be validated by the author(s) of the published studies or by the CBB to maintain CB unit viability and potency during the required storage at the CB Collection Site.

Evidence:

The inspector should review the validation studies, and verify the validated processes are used consistently.

CB units must not be stored in areas where temperature is uncontrolled, such as in closets that are not serviced by the facility's heating and cooling system or in areas with exposure to direct sunlight.

Example(s):

Examples of validating the temperature range during storage at the CB Collection Site include a) testing whether cells remain viable under extreme temperatures (especially high temperatures) experienced in storage areas or b) demonstrating that the storage area is climate-controlled and able to maintain expected temperature range.

STANDARD:

C6.8 The chain of custody of the CB unit shall be maintained from collection to receipt at the CBB.

Explanation:

Chain of custody is the process of ensuring and providing documentation of proper CB unit identification and handling from the time of collection to the receipt at the CBB.

This protocol assures:

- The CB unit belongs to the individual whose information is printed on the CB unit label,
- no adulteration or tampering has taken place,
- exactly who had possession of the CB unit and when,
- how the CB unit was distributed and stored before it was analyzed,
- no unauthorized access to the CB unit was possible,
- the CB unit was handled in a secure manner.

STANDARD:

C6.9 *Records shall be maintained at the CBB of all reports of adverse events that occur during or immediately after CB collection.*

Example(s):

Records of adverse events may be maintained in the hospital but must be shared with the CBB for evaluation, trending, and possible corrective action. It is common that collection adverse events (for example, needle sticks) will be reported and managed by the hospital's employee health or risk management processes. The CBB must have a means to collect information related to the frequency and severity of such incidents.

C7: TRANSPORTATION AND SHIPPING OF UNMANIPULATED CORD BLOOD UNITS BETWEEN THE CORD BLOOD COLLECTION SITE AND THE CORD BLOOD PROCESSING FACILITY

STANDARD:

C7.1 *Transport and shipping of CB units shall be in compliance with Applicable Law.*

C7.2 *The methods of transport and shipping of the CB unit between the CB Collection Site and the CB Processing Facility shall be designed to protect the integrity of the CB unit and the health and safety of personnel.*

Evidence:

The transportation and shipping process described by the facility should account for variables such as time, temperature, and type of container. This includes conditions during storage prior to shipping.

STANDARD:

C7.3 *The primary CB collection bag shall be placed in a sealed secondary plastic bag to contain any leakage from the primary bag.*

C7.4 *The CB unit shall be transported or shipped with required accompanying records as defined in Standard Operating Procedures.*

Explanation:

The records that should accompany the CB unit at transportation or shipment depend on the methods in place at the CBB and the CB Collection Site. The Standards are not prescriptive, but require the CB Collection Site to determine the records that must be sent with the unit. At a minimum, the required accompanying information as listed in Appendices I and II must accompany the unit or be included on the affixed or attached label.

Example(s):

The records required for a fixed CB Collection Site may be different than those for a collection kit model. The informed consent process also makes a difference; for example, if the process is a two-step process, much of the information is most likely already at the CBB.

STANDARD:

C7.5 *CB units shall be placed in an outer container that is qualified to maintain a designated temperature range around the CB unit to protect cell viability during CB unit transport and shipping.*

C7.5.1 *The immediate environment shall be made of material adequate to withstand leakage of contents, shocks, pressure changes, and other conditions incident to ordinary handling during transportation and shipping.*

Evidence:

There should be robust qualification of the transport/shipping container to cover all scenarios of environmental conditions. Information regarding the qualification process can be found in the QM Plan and SOPs, and with documentation of the validation study itself.

STANDARD:

C7.5.2 *The process for transport and shipping shall be validated to maintain a designated temperature range in the immediate environment of the CB unit.*

C7.5.3 *When a CB unit is shipped, the temperature inside the immediate environment shall be continuously monitored, or the unit shall be shipped in a rigorously validated container.*

Explanation:

Containers used to transport and ship CB units must be thermally-insulated and sturdy enough to sustain regular usage without damage to the units. They should be designed in a manner so as to maintain a predictable temperature range regardless of environmental conditions. Gel packs or other temperature stabilizing materials may be used, if part of the usual SOP. All containers must be validated for temperature extremes appropriate for the geographical location(s) where the CB is collected and shipped. Validation must include temperatures during storage and transportation. Each individual transport or shipping container must be validated. Additional containers of the same make and model previously validated may undergo slightly less rigorous verification after several validations, if appropriate.

Temperature ranges must be specified, even where room temperature is the designated temperature.

The Standards distinguish between transport and shipping based upon whether a CB unit is distributed via trained personnel (transport) or when it is distributed via unattended freight (shipping, such as via FedEx trucks or airplanes). It is not necessary to continuously monitor the temperature of a validated container that is transported by trained personnel who understand how to minimize exposure to extreme temperatures and can recognize when the temperature may have been compromised.

In general, continuous monitoring of temperature inside the transport container when a CB unit is shipped provides the most reliable certainty that the CB unit has not been exposed to detrimental temperatures. There are few, if any, transport containers adequately validated to justify shipment of CB units without continuous temperature monitoring. However, if a bank chooses to validate such a shipping container, a rigorous validation study is required, including the following minimum elements at a minimum:

- Time: The shipping container must be validated to maintain the specified temperature range for at least 4 hours beyond the maximum time required to reach the CBB laboratory.
- Replicates: The entire validation must be done with a minimum of three units at each temperature and distance, in primary containers of the same materials used in routine collections, and varying in size from smaller than the smallest acceptable unit to at least as large as the largest received. Various cell concentrations must be included, and these data recorded.
- Temperature: The studies must encompass environmental temperatures within 10 degrees C of the coldest and the hottest temperatures recorded in recent years in the geographical area. This may require testing during different seasons.
- Shipping: The units must actually be shipped by the methods in use, over the distances and times that will be used by the bank. For example, if units will be shipped by commercial air flights, the validation studies must include such shipment in replicates. The same holds for taxi, train, truck, or other vehicles.
- End points: Acceptance criteria must include several assays of cell recovery, such as TNC or CD34 cell recovery. At least one acceptance criterion must be a functional assay such as CFU or viable CD34 recovery. Lack of contamination during shipment must be included.
- Conclusions: All units must pass the acceptance criteria for the validation study to be considered successful.

Section B (Standard B2.14.2) describes appropriate preparation and approval of the validation plan, which should be followed. The shipping container should be inspected for damage when it is returned to the CBB, and the ability to maintain appropriate temperature should be verified between uses. The process validation is expected prior to shipment of units, and the process should be repeated when there is a significant change in the process.

In addition, the CBB must have acceptance criteria for all CB units prior to processing including verification of temperature inside the container. If related donor units are received that do not meet acceptance criteria, the CBB must notify the family donors.

Example(s):

Examples of significant changes that require revalidation include:

- Type of vehicle.
- Duration of transport or shipping.
- Temperature range.

There are a variety of ways to record the parameters of continuously monitored temperatures, including:

- Minimum/maximum thermometers,
- Devices that take intermittent sample readings of temperatures,
- Continuous data loggers.

STANDARD:

C7.6 The outer container shall be labeled with the information required in the Cord Blood Unit Labeling table in Appendix II.

C7.6.1 The outer container shall be secured.

Example(s):

The outer container may be secured through a locking mechanism, an anti-tampering seal, or some other method that minimizes the risk of accidental or purposeful opening of the container.

STANDARD:

C7.7 Transportation and Shipping Records.

C7.7.1 A list identifying each CB unit and its associated samples, maternal samples, and documents that are enclosed in a package shall be included.

C7.7.2 Transportation and shipping records shall permit the tracking of the CB unit from the CB Collection Site to its final destination.

C7.7.3 Transportation and shipping records shall include:

C7.7.3.1 The CB Collection Site responsible for transporting or shipping the CB unit.

C7.7.3.2 The date and time of transport or shipment.

C7.7.3.3 The identity of the courier.

C7.7.3.4 The date and time of receipt of the package.

C7.7.3.5 The condition of the package upon receipt.

Explanation:

The list identifying items enclosed in a package should clearly state what the CB Processing Facility should have received. This includes:

- Name or identifier of collection site,
- Quantity of CB units included in each container,
- How many containers were shipped,
- Records that allow identification of each individual CB unit.

Example(s):

The following is an example of a form that could be used to document transport and shipping information:

Collection site ID: _____

Total containers shipped: _____

Container ID	Number of units	Unit ID
A	2	CBx-112233
		CBx- 112234
B	1	CBx- 00007

Packed by : Carol*

Date and Time of departure: 04/18/12 at 7:35

Courier name: Joe*

Date of arrival at processing facility: 04/18/12_____

Received by: Jane* at 19:30

Condition of the container:_____

* (signatures and initials on file.)

CORD BLOOD PROCESSING STANDARDS

PART D

- D1 Facility Requirements
- D2 Policies and Standard Operating Procedures
- D3 Cord Blood Processing
- D4 Samples
- D5 Cryopreservation
- D6 Conditions for Storage
- D7 Monitoring and Alarm Systems
- D8 Disposition
- D9 Cord Blood Unit Testing
- D10 Maternal Testing

PART D: CORD BLOOD PROCESSING STANDARDS

D1: FACILITY REQUIREMENTS

STANDARD:

D1.1 The CB Processing Facility shall be licensed, registered, or accredited as required by the appropriate governmental authorities for the activities performed.

Explanation:

National laws and regulations may require registration or licensure by the government or may require accreditation from professional organizations for the activities performed within the facility. In some countries, the actual CB units may also require licensure.

Evidence:

The inspector will be provided with documentation or other evidence of the registration, licensure, or accreditation of the CB Processing Facility with all applicable regulatory or government agencies. Copies of the relevant documentation must be submitted in advance.

If such documentation is not provided prior to the inspection, the inspector may ask to see it on site. The CB Processing Facility Director should know who in the institution is responsible for the registration, and where a copy may be obtained. It is not appropriate to request a faxed copy from the regulatory agency during the on-site inspection.

Example(s):

Examples of requirements include FDA registration in the U.S., TGA license in Australia, and similar requirements in Europe and elsewhere.

If a CBB is in the U.S., it must be registered in accordance with 21 CFR part 1271. The timing of registration should be within 5 days after beginning operations (21 CFR part 1271.21). If a bank outside the U.S. exports CB units to the U.S., it must be registered with the FDA and also have a U.S. agent. Note that each activity performed by the institution must be registered, regardless of who performs the activity. A CB Processing Facility that is within a larger institution such as a hospital or medical center may combine its registration with other services. More information regarding registration with the FDA can be found at

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/EstablishmentRegistration/default.htm> U.S. CBBs must also have an approved BLA or IND for distribution of unrelated CB units.

In the EU, the competent authorities in the Member States ensure that all tissue establishments have been accredited, designated, authorized, or licensed and that these establishments have implemented the EU Directive, other national regulations, or both where applicable.

In Australia, an appropriate license for the manufacture of HPC, Cord Blood issued by the TGA is required.

Other countries' requirements must be followed in accordance with their laws and regulations.

STANDARD:

D1.2 There shall be designated facilities of adequate space, design, and location for the intended procedures.

D1.2.1 The designated facilities shall be divided into defined areas of adequate size to prevent mix-ups, mislabeling, contamination, or cross-contamination of CB units during the following activities:

D1.2.1.1 Preparation of, and safe, sanitary, and orderly storage of, the equipment, supplies, and reagents needed for processing, testing, cryopreservation, storage, and release.

D1.2.1.2 Processing activities and ancillary functions.

D1.2.1.3 Storage of CB units prior to release or distribution.

D1.2.1.4 Maintenance of records.

Example(s):

One method of preventing sample mix-ups in the CB Processing Facility is to process only one CB unit at a time in one biological safety cabinet.

STANDARD:

D1.3 The CB Processing Facility shall be secure in order to prevent the entrance of unauthorized personnel.

Explanation:

The CB Processing Facility must be secure to prevent unauthorized personnel from entering the facility. If the facility consists of shared space between CB unit processing and another function, for example, research, all aspects of the facility that affect CB units must be segregated and be in compliance with these Standards.

The use of shared equipment is discouraged. If equipment is shared, it must be used and maintained in compliance with these Standards at all times, including when it is used for purpose other than processing cord blood units. This is because the maintenance and use of the equipment has a direct impact on the quality of units.

Evidence:

The inspector should pay attention to the ease with which he/she enters the facility as a measure of facility security. The inspector will look for technological security measures or a method of ensuring only people with permission enter the facility. In addition to securing the entrance of the CB Processing Facility, the daily operations, equipment, and records must also be secure.

Example(s):

The CBB may use technological methods to secure the facility, such as the use of electronic badge scanners, or manual methods such as a list of authorized personnel, the use of visitor registers, and a policy that non-processing personnel are accompanied by processing personnel while in the facility.

STANDARD:

D1.3.1 The CB Processing Facility shall have oversight of non-processing personnel visiting the CB Processing Facility to maintain compliance with these Standards.

Explanation:

Persons who are not employed by the CBB may be present in or routinely enter the CB processing area. When repair technicians or delivery personnel enter the CB Processing Facility, the CB Processing Facility staff must oversee these individuals to confirm their activities are in compliance with the standards relevant to their activities in the facility.

Example(s):

Environmental conditions, equipment cleanliness, and the use of facility space are examples of ways that personnel not employed by the CBB can affect the safety of CB units.

STANDARD:

D1.4 The CB Processing Facility shall provide adequate lighting, ventilation, air quality, and access to hand decontamination to ensure adequate conditions for proper operations in compliance with Applicable Law.

D1.5 The CB Processing Facility shall be maintained in a clean, sanitary, and orderly manner.

D1.5.1 There shall be documentation of facility cleaning and sanitation.

Explanation:

CB Processing Facility cleaning and sanitation must be performed and recorded on a regular basis in order to prevent contamination and cross-contamination of CB units. While the bench-top, biological safety cabinet, and equipment surfaces are most often cleaned and disinfected by facility personnel, other surfaces (such as floors, walls, and ceilings) may be cleaned by outside vendors. These services are included under this standard. Responsibility should be assigned for personnel performing the cleaning and sanitation procedures, the methods used, and the schedule.

Evidence:

The CB Processing Facility shall have procedures that detail methods for facility cleaning and the maintenance and inspection of environmental conditions. Documented evidence of facility cleaning, including that performed by outside personnel, must be maintained and available for review by the inspector.

Example(s):

The facility may have a checklist for outside vendors performing cleaning/sanitization tasks that is signed and dated upon completion.

STANDARD:

D1.6 CB Processing Facility environmental conditions that affect the safety and potency of the CB unit, including temperature; humidity; ventilation; and air pressure, filtration, and classification, shall be defined, and as appropriate for the degree of classification, controlled, monitored, and recorded to demonstrate ongoing compliance.

Explanation:

Facility requirements differ based upon Applicable Law (such as EU, FDA, and TGA) and clean room designation. The CBB must identify the parameters that should be controlled and monitored based on their potential effect on CB unit quality. Environmental considerations include temperature and humidity control, ventilation and air filtration, and sanitation of the room and equipment at appropriate times. Environmental monitors such as measures of air quality (e.g., viable and non-viable particle counts), and control of humidity and temperature can be used to minimize airborne contaminants. There must be ongoing monitoring of any parameters that have been determined to be critical; these should be defined by an SOP, and compliance should be evident through quality records.

Clean rooms with specified air classification are not required by these Standards; however, this standard is a minimum requirement. Individual countries may have more stringent regulations that must be followed.

Evidence:

Each facility should assess the risk of environmental conditions on the safety and potency of the CB unit, depending on specific processes and the results of process validations. The assessment should be documented. Records of environmental conditions such as temperature and humidity and their review should be available for review by the inspector.

Example(s):

The CB Processing Facility may have a continuous monitoring system that facilitates periodic review of recorded data, such as room temperature and humidity.

The CB Processing Facility may not require a classified environment provided that the processing steps requiring exposure to the environment are performed in a biological safety cabinet. However, a facility that extensively manipulates CB and performs procedures with many “open” steps may require a greater level of environmental control. Local or regional guidelines may have more specific requirements such as adherence to the principles of Good Manufacturing Practice (GMP). Contaminants in the CB Processing Facility can be minimized through air filtration and by ensuring that the air pressure within the facility is positive to the surrounding area. The claim for positive air pressure requires use of room pressure monitors.

In the EU, where products are exposed to the environment during processing, an air quality with particle counts and microbial colony count equivalent to those of Grade A is required with a background environment appropriate for the processing of the cellular therapy product, but minimally equivalent to GMP Grade D in terms of particles and microbial counts. See the European Commission Directive 2006/86/EC and EU Guidelines to Good Manufacturing Practice (GMP), Annex 1 01 March 2009.

STANDARD:

D1.7 *Personnel Safety Requirements.*

D1.7.1 *The CB Processing Facility shall have Standard Operating Procedures that utilize universal precautions and are also designed to minimize risks to the health and safety of employees, volunteers, and visitors, including at least:*

Explanation:

This standard requires appropriate protection in place for those entering or proximate to the CB Processing Facility. Facilities must define the risks, minimize those risks, and have procedures for how to respond to exposure to potential contaminants.

The CB Processing Facility must have defined plans for responding to each of the hazards listed, including fire within or adjacent to the processing and laboratory areas. The facility policies and SOPs, including housekeeping and waste disposal, must document compliance with good biosafety procedures, including adherence to universal precautions and to Applicable Laws regarding safety.

The facility should have a safety manual. A CBB may utilize an institutional safety manual if there is written documentation of how the safety manual is reviewed and kept updated with institutional revisions. Safety, infection control, or biohazard waste disposal procedures that are unique to the CB Processing Facility should be covered in a CB Processing Facility SOP Manual that augments the institutional manual. 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 CB 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.

If processing is underway during the day of inspection, the inspector will observe personnel for use of protective clothing and other biosafety precautions. If no processing procedures are conducted that day, a mock procedure should be demonstrated. Employee files must document review of safety procedures and compliance and training in biological, chemical, and radiation safety (when appropriate). How CB units are handled and discarded (e.g., incinerator, waste field, etc.) must match the written protocols. Compliance with federal, national, and state regulations should be addressed by the facility. The presence of unused equipment, excessive traffic from unauthorized personnel, or inappropriate storage of reagents and supplies may also contribute to an unsafe environment and should be reviewed.

Evidence:

The inspector should see instructions for personnel actions in the case of exposure to hazardous agents or if a fire alarm sounds. Posted routes for exiting the facility should also be used.

Example(s):

Safety training records for CB Processing Facility personnel, including universal precautions for handling blood and biological substances, should be created and available for inspection. Safety training may be provided as an individual training session or be addressed as a component of task-specific training. Training in universal precautions per the Center for Disease Control for handling blood is a requirement of the OSHA in the U.S.

STANDARD:

- D1.7.1.1 Bloodborne pathogens.*
- D1.7.1.2 Hand washing and/or decontamination.*
- D1.7.1.3 Chemical hazards.*
- D1.7.1.4 Liquid nitrogen, including oxygen levels.*

Explanation:

When liquid nitrogen is used in the Processing Facility, proper ventilation and the use of oxygen sensors are required. The risk of asphyxia must be assessed wherever liquid nitrogen is used or stored. A low oxygen sensor will alert staff when there is an oxygen-deficient atmosphere in the room.

STANDARD:

- D1.7.1.5 Latex allergy.*
- D1.7.1.6 Radiation safety, if applicable.*

Example(s):

If a CBB is near a blood bank or within a hospital-based institution, personnel may be exposed to radiation and, therefore, the CBB is responsible for establishing procedures for radiation safety.

STANDARD:

- D1.7.1.7 Fire safety.*

Example(s):

Documented reports of fire drills demonstrate an acceptable plan for fire safety.

STANDARD:

- D1.7.1.8 Power failures.*
- D1.7.2 Gloves and protective clothing shall be worn while handling biological specimens. Such protective clothing shall not be worn outside the work area.*

Explanation:

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 CB units. The type of exposure that may be encountered will determine the appropriate suitable protection.

STANDARD:

D1.7.3 The CB Processing Facility shall have written policies and procedures for action in case of exposure to communicable disease agents or to chemical, biological, liquid nitrogen, or, if applicable, radiological hazards.

D1.7.4 Medical waste shall be disposed of in a manner to minimize hazard to facility personnel and the environment in accordance with Applicable Law.

Explanation:

Any potentially biohazardous material shall be discarded in a safe manner according to written protocols for the disposal of biohazard waste. Radioactive waste must be discarded using methods approved by appropriate governmental agencies. Also, CB Processing Facilities should post warning signs wherever radioactive materials are in use. Facility personnel responsible for these activities shall be identified.

Example(s):

Contaminated materials may be discarded by autoclaving, ultra-high temperature incineration, decontamination with hypochlorite solution, and, in some locations, the use of a landfill. Sharps like needles, blades, etc., whether or not they are infected, should be considered highly hazardous health care waste and placed for disposal in puncture proof containers.

STANDARD:

D1.7.5 Oxygen levels should be monitored wherever liquid nitrogen is in use.

D2: POLICIES AND STANDARD OPERATING PROCEDURES

STANDARD:

D2.1 The CB Processing Facility shall establish and maintain policies and/or Standard Operating Procedures addressing critical aspects of operations and management in addition to those required in B2. These documents shall include all elements required by these Standards, shall be consistent with the policies and Standard Operating Procedures of the CBB, and shall address at a minimum:

Explanation:

The intent of this standard is that each step in the life of a CB unit from unit acquisition to final disposition is documented and performed in a consistent manner in order to ensure the quality, safety and potency of units collected, banked, stored, and released for administration.

The CB Processing Facility must comply with the requirements for SOP management specified in B3. It is possible that the CB Processing Facility Director may be different than the CBB Director, or that the facility is a contracted facility; however, the SOP scheme must still meet these Standards. This includes required elements of each individual SOP, ability of personnel to access the SOPs at all times, personnel compliance with SOPs, and review and approval of the CBB Director or designee.

Evidence:

Inspectors are provided with the CB Processing Facility's key policies and SOPs prior to visiting the facility to allow observation of conformance of personnel performance with the defined policies and procedures.

STANDARD:

- D2.1.1 *CB unit acceptance criteria, processing, cryopreservation, and storage.*
- D2.1.2 *Maternal testing.*
- D2.1.3 *Process control, including product specifications and nonconforming products and processes.*
- D2.1.4 *Labeling of the CB unit and all samples and documents.*
- D2.1.5 *Storage of all samples.*
- D2.1.6 *Acceptable levels of hemodilution of maternal samples used for communicable disease testing.*
- D2.1.7 *Communicable disease testing, microbial cultures, HLA typing, hemoglobinopathy testing, and other testing. Acceptance criteria for test results shall be described.*
- D2.1.8 *Criteria for release of CB units from quarantine, including nonconforming CB units.*
- D2.1.9 *HLA typing to include requirements for resolution, loci, timing, and verification.*
- D2.1.10 *Electronic record entry, verification, and revision.*
- D2.1.11 *CB unit records.*
- D2.1.12 *CB unit disposition.*
- D2.1.13 *Personnel training and continued competency for the procedures performed.*

Explanation:

Processing personnel must hold relevant education and experience and be appropriately trained to demonstrate competency in the tasks they are required to perform within the CB Processing Facility. This also applies to facilities that are contracted to perform CB unit processing activities for the CBB.

For personnel who do not process CB units, the CB Processing Facility should also have documentation of their training and competency for the tasks they are required to perform within the CB Processing Facility that have a direct or indirect impact on the safety, quality, identity, purity, or potency of the product or its related service.

Specific requirements for key CB Processing Facility personnel are in Appendix I. Section B also requires adequate staff for all assigned operations.

Evidence:

The records of training and competency assessment for all Processing Facility personnel should be available for review by the inspector.

STANDARD:

- D2.1.14 *Facility management including a description of environmental monitoring.*
- D2.1.15 *Materials management.*
- D2.1.16 *Equipment monitoring, qualification, and maintenance.*
- D2.1.17 *Cleaning and sanitation procedures including identification of the individuals responsible for the activities.*
- D2.1.18 *Disposal of medical and biohazardous waste.*
- D2.1.19 *Hygiene and use of personal protective attire and equipment.*
- D2.1.20 *Emergency and safety procedures.*
- D2.1.21 *Biological, chemical, and, if applicable, radiation safety.*
- D2.1.22 *A disaster plan to provide for continuous safe storage and transport and shipping, if applicable, of the CB units.*

Explanation:

How the CBB deals with the scope of possible events that constitute real threats to personnel and inventory must be described. The plan should identify internal disasters (such as loss of vacuum in a liquid nitrogen tank) and external disasters (such as loss of power in a building structure in severe weather or other natural event). Community or regional disasters would necessitate a more comprehensive strategy, one that a facility may not have all the details for but should at least have considered. The plan should also indicate that any event requiring transfer of inventory or exposure of CB units to temperatures outside the CBB's prescribed ranges must be documented.

Example(s):

Examples could include transferring inventory from a compromised storage vessel to an alternative tank within the facility or in a neighboring facility if such an agreement or facility exists.

STANDARD:

D2.1.23 Disposal of a CB unit.

D2.2 All CB Processing Facility personnel shall comply with these Standards and policies and Standard Operating Procedures.

D3: CORD BLOOD PROCESSING

STANDARD:

D3.1 Acceptance Criteria.

D3.1.1 Upon receipt of a CB unit package into the CB Processing Facility, the contents of the shipping container shall be inspected for the following at a minimum:

D3.1.1.1 Receipt within an acceptable amount of time as defined by the CBB.

D3.1.1.2 The integrity of the outer container and the temperature against validated parameters.

D3.1.1.3 Verification of the contents against the list of enclosed items.

D3.1.1.4 The CB unit for appropriate appearance, integrity, labeling, and identification.

D3.1.1.5 The associated samples, maternal samples, and documents for appropriate labeling and identification.

D3.1.2 For unrelated CB units, an appropriately signed consent authorizing processing, testing, and storage of the CB unit and samples for the intended purpose shall be confirmed before processing is completed.

D3.1.3 For related CB units, there shall be a signed agreement with the donor family for collection, processing, testing, storage, disposal, and the name and contact information of the donor family.

D3.1.4 If a CB unit collected for related use may subsequently be released for unrelated use, there shall be informed consent for such release obtained before processing.

Explanation:

CBBs must verify CB units meet established quality criteria upon arrival at the CB Processing Facility. One metric that may be used to determine that sample quality was maintained is assessing the temperature of the shipping container upon arrival.

In a distributed kit model in which collection kits may be stocked within physician's offices and birthing centers, the ability to effectively utilize temperature monitoring devices is limited. Additionally, having

the ability to monitor the temperature of the collection kit contents during transit to the manufacturing facility doesn't prevent temperature excursions; it simply provides visibility as to whether or not such a temperature excursion occurred. If a CBB has validation data to support the ability of the collection kit to mitigate a negative impact on sample quality, evaluating the quality of every sample against pre-defined quality metrics upon receipt can suffice. If a CB unit does not meet pre-defined quality metrics upon receipt, the CBB must have policies and procedures that define when these units will be maintained in inventory. In the case of related donor units, these policies must include notification of the family that the unit did not meet quality metrics upon receipt.

For related CB units, the signed agreement should include the name of the intended recipient if applicable. This may not be applicable to some CB units that are stored at the request of a donor family to be used in the future for purposes not known at the time of the agreement. The release of related CB units shall be covered under directed donation as defined at the time of collection/storage by the CBB's policies/procedures.

A validated electronic signature is acceptable for written agreements and informed consent.

Example(s):

The U.S. FDA regulations do not provide a mechanism for crossing over products intended for related use to use by an unrelated recipient. Therefore, D3.1.4 does not apply to CB units manufactured in or imported to the U.S.

STANDARD:

D3.2 Processing.

- D3.2.1 CB units shall be properly labeled and clearly identified prior to acceptance for processing.*
- D3.2.2 CB units shall be labeled during all stages of processing with an attached partial label at a minimum.*
- D3.2.3 Information regarding processing steps that have been completed on a CB unit shall accompany the CB unit or be available electronically during all stages of processing.*
- D3.2.4 Processing and cryopreservation of CB units shall be performed according to Standard Operating Procedures validated to result in acceptable viability, recovery, and potency.*

Explanation:

The CB Processing Facility Director should determine what and how processing methods will be validated. Validation may be retrospective, concurrent, or prospective. Validation should include evaluation of processing results, data analysis, establishment of expected ranges, means, medians, and periodic documentation that the procedure is continues to yield results within the expected range. This verification may be best performed at the time of SOP review.

New procedures introduced into the CB Processing Facility should undergo prospective validation when possible. Prospective validation of a processing procedure may be accomplished by performing

mock procedures using surrogate CB units. If insufficient numbers of surrogate units are available, validation studies may be performed using portions of a unit and a scaled-down procedure.

A robust validation study meets the following criteria:

- A validation plan was written prior to the study, and was approved by the Processing Facility Director and the quality unit at a minimum prior to its execution.
- The validation plan includes the purpose of the study, the samples to be assessed, the tests to be performed, the relevant SOPs to follow, and the expected results (acceptance criteria).
- The minimum number of assays is sufficient to establish a high level of probability that the results are reproducible.
- The assays assess the extreme conditions of time, temperature, and any other variable that exists in normal conduct of the procedure.
- The results must all meet acceptance criteria. If acceptance criteria have not been met, the process cannot be considered to be validated.

Ultimately, validation of the quality of the unit is determined by timely engraftment of the transplanted cells and the clinical outcome of the recipient. However, often only a small fraction of stored CB units are released and transplant outcomes data is not available for all released units. Therefore, CBBs may employ a surrogate functional potency assay to demonstrate the validity of process control (including processing, cryopreservation, and storage of CB units) demonstrating preservation of functional potency (e.g., CFU or viable CD34).

When CB is used for regenerative medicine or other indications, unit quality may be assessed by viability of thawed cells, by specific functional assays, or both. For all units, there should be *in vitro* studies to assess whether the desired end-point of the processing procedure was achieved.

In some cases, the CB Processing Facility may implement a processing procedure or process that has been validated by another facility or has been published in the peer-reviewed medical literature. In such cases, a robust validation may not be necessary. The facility may need only to verify that the procedure or process results in comparable results when performed locally. It remains important that a formal process be followed and that objective acceptance criteria have been established.

Evidence:

The inspector must review one or more validation or verification studies to determine if the requirements of these Standards are met.

End-points and specifications may be based on in-process results or on final CB units.

STANDARD:

D3.2.4.1 Critical control points shall be identified and their specifications defined.

Explanation:

The CBB must define certain points during processing and cryopreservation at which personnel must verify the in-process end points have been achieved.

Example(s):

A CBB may document that critical control points have been verified using a checkbox on a worksheet, requiring the initials of the verifying personnel, or using electronic systems.

Examples of end-points include the following:

- A minimum threshold for nucleated cell yield after processing (for example, percent recovery or total count)
- Post-processing CD45 and/or CD34 viability
- Potency/CFU assays with a defined quantitative or qualitative endpoint
- CD34 cell content
- Target limit for final volume after processing
- Maximum time between collection and freezing, between start of processing and cryopreservation, and between addition of DMSO and cryopreservation
- Predetermined acceptance criteria for cryopreservation (freezing curve).

STANDARD:

D3.2.4.2 Failure of the processing procedure to achieve specifications for critical control points shall be evaluated with appropriate action documented.

Explanation:

If a CB sample fails to meet defined specifications at pre-determined critical control points, the CBB must evaluate whether or not the CB unit still meets requirements for storage.

STANDARD:

D3.2.5 Methods for processing shall employ aseptic technique, and CB units shall be processed in a manner that minimizes the risk of mix-ups and cross-contamination.

Explanation:

The simultaneous presence of CB units from more than one donor in a CB Processing Facility is a frequent occurrence. Procedures must be in place to prevent the possibility of mix-ups or cross-contamination of units in such circumstances. Procedures must define safeguards to be employed (such as forbidding units from more than one donor to be in a Biological Safety Cabinet at any one time) and must include the cleaning and sanitation practices to be used for sequential processing using the same equipment. Often two or more CB units are simultaneously cryopreserved or placed in a controlled rate freezer. The CBB must have a policy or procedure to safeguard against errors in labeling and possible mix-up of CB units.

Evidence:

The inspector should observe the CB Processing Facility in operation and should ask personnel what processes are in place when multiple CB units are received into the facility on the same day. The inspector should determine (from direct observation and by reviewing SOPs) that aseptic technique is utilized during processing.

Example(s):

Other methods to prevent mix-ups may include identification of reagents as dedicated to a single processing procedure and a separation of records to avoid a mix-up of information.

STANDARD:

D3.2.5.1 Where processing of CB units is not in a closed system, processing shall take place in an environment with specified air quality and cleanliness.

Explanation:

Whenever possible, closed systems should be used for all processing steps. This is important to reduce the likelihood of microbial contamination during processing, and of cross-contamination with other infectious agents or cells from other CB units.

GTP regulations specifically forbid the pooling of HCT/Ps from more than one donor during processing. For dual cord blood transplants it is acceptable to sequentially thaw and infuse products from different donors, but it is not acceptable to pool the products into a single container for infusion. For some CB units processed as specified in IND, IDE, or an equivalent regulatory approval pathway, pooled cells may be part of the manufacturing process. If reviewed and approved by the regulatory authority, these processes are permitted under these Standards.

Example(s):

In the EU, if cells are exposed to the environment during processing, 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, is required.

STANDARD:

D3.2.5.2 The effectiveness of measures to avoid contamination and cross-contamination shall be verified and monitored.

D3.2.6 Cryopreservation of unrelated CB units shall be initiated within 48 hours of CB collection.

D3.2.7 Cryopreservation of related CB units shall be initiated within 72 hours of CB collection.

Explanation:

The distance between CB collection and processing centers may be significant, and can vary significantly. Determining the maximum time between collection and the start of processing and cryopreservation without compromising the functional potency of the CB unit is crucial. Ideally, CB units should be processed as soon as feasible; however, some delays are unavoidable. Based on published literature, FACT standards allow initiation of processing for unrelated units within 48 hours of collection; and for related donor units within 72 hours of collection. Any exceptions must be validated or justified by the CBB. Current data support CB unit storage and transport using a temperature of $\sim 4^{\circ}\text{C}^{1-3}$. Recovery of MNC, viable CD45 cells, CD34 cells, and CFU was preserved in most studies until 48 hours after collection, with a tendency to decline after 24 to 48 hours¹⁻³. Some studies suggest that viable CD34 cells and CFU are preserved until 72 to 96 hours post-collection⁴. However, caution must be exercised regarding the maximum time allowed from collection to processing until definitive data are available

that demonstrate CB units processed more than 48 hours after collection are still capable of hematopoietic reconstitution in humans. Currently, most studies have utilized *in vitro* studies such as viable CD34 cell count and CFU growth. Since these *in vitro* studies cannot yet fully predict *in vivo* hematopoietic reconstitution outcome, these assays should be interpreted with caution. Recently, one study has shown that CB stored at room temperature for 72 hours, processed, cryopreserved, and thawed maintained CFU potency, yet failed to reconstitute hematopoiesis in a surrogate animal transplant model, suggesting a discrepancy between *in vitro* and *in vivo* assays⁵.

References Cited:

1. Hubel A, Carlquist D, Clay M, McCullough J. Short-term liquid storage of umbilical cord blood. *Transfusion*. 2003 May; 43(5):626-32.
2. Hubel A, Carlquist D, Clay M, McCullough J. Liquid storage, shipment, and cryopreservation of cord blood. *Transfusion*. 2004 Apr; 44(4):518-25.
3. Kurtzberg J, Cairo MS, Fraser JK, Baxter-Lowe L, Cohen G, Carter SL, Kernan NA. Results of the cord blood transplantation (COBLT) study unrelated donor banking program. *Transfusion*. 2005 Jun; 45(6):842-55.
4. Pereira-Cunha FG, Duarte AS, Reis-Alves SC, Olalla Saad ST, Metze K, Lorand-Metze I, Luzo AC. Umbilical cord blood CD34(+) stem cells and other mononuclear cell subtypes processed up to 96 h from collection and stored at room temperature maintains a satisfactory functionality for cell therapy. *Vox Sang*. 2014 Oct 21.
5. Louis I, Wagner E, Dieng MM, Morin H, Champagne MA, Haddad E. Impact of storage temperature and processing delays on cord blood quality: discrepancy between functional *in vitro* and *in vivo* assays. *Transfusion*. 2012; Nov; 52(11):2401-5.

Due to the nature of related CB units, CBBs are expected to fulfill contractual obligations with the donor families. However, private CBBs should set goals and metrics to facilitate processes and provide donor family instructions that result in quality units. Therefore, in private banking, cryopreservation must be initiated within 72 hours of CB collection. CBBs must have policies to notify the donor family if this end point is not met.

Evidence:

The inspector should review processing and cryopreservation records to determine that policies and SOPs are in place and followed to initiate cryopreservation within the defined time period. Examples of such documentation may include CBB processing trend analyses that demonstrate range of time elapsed from collection to start of cryopreservation. If CB samples are not cryopreserved within the pre-defined timeframes noted above, the CBB should note this deviation and address it according to their facility protocols.

Example(s):

The delay of a related CB unit from a family due to a snowstorm is an example of a single deviation that may be accepted by the CBB and documented in accordance with its QM Plan.

STANDARD:

D3.2.8 More than minimal manipulation of a CB unit shall be performed in accordance with Applicable Law and:

- D3.2.8.1 *Using reagents and/or devices approved for that manipulation by the appropriate governmental agency or*
- D3.2.8.2 *With an Institutional Review Board or Ethics Committee-approved protocol or*
- D3.2.8.3 *With an active approved Investigational New Drug Application, Investigational Device Exemption, or non-U.S. equivalent.*

Explanation:

More than minimal manipulation occurs when cells are manipulated in a way that alters the biological characteristics of the cell population.

Evidence:

If possible, the inspector should observe the processing of CB units and verify that processing personnel are adhering to the validated or verified policies and procedures set forth in the SOP.

Example(s):

More than minimal manipulation includes, but is not limited to, cell expansion, activation, and genetic modification. Documentation of relevant regulatory approval should be available for on-site review by the inspector.

STANDARD:

- D3.2.9 *Equipment, supplies, and reagents shall not adversely affect the viability of the CB units and shall not permit the introduction of adventitious agents or the transmission or spread of communicable disease.*

Evidence:

Equipment qualification records, materials management procedures, and process validation studies must include consideration of the potential effect on the viability and sterility of the processed CB unit.

STANDARD:

- D3.3 *At the completion of processing prior to cryopreservation, the freezing bag shall be labeled with the information as required by the Cord Blood Unit Labeling table in Appendix II.*

D4: SAMPLES

STANDARD:

- D4.1 *At a minimum, the following samples shall be collected from the CB unit prior to cryopreservation:*

Explanation:

These requirements apply to all CB units (unrelated and related) unless otherwise specified.

Evidence:

The inspector will verify in SOPs or policies how many and what type of samples the CBB routinely obtains.

STANDARD:

D4.1.1 A target minimum total volume of at least 200 μ L divided into at least two (2) segments with each sealed and integrally attached to each freezing bag.

Explanation:

These reference samples are stored as segments because the tubing from which they are made shares the same fluid path as the CB unit, and therefore the contents of these segments should be identical to the unit, and thus be reliable to assess identity and potency. These Standards are intended to allow flexibility to allow innovation in this area, as long as the material is confined within tubes or containers that are integrally attached to the unit. If a single unit is stored in two separate bags, each bag must have two integrally attached segments. Cell concentration may be different among unit samples, and should be taken into account when determining the needed sample volume.

The concept behind the use of this material is that it best represents the cryopreserved CB unit. The material within the segments has undergone the identical collection, processing, cryopreservation, and storage conditions as the unit. Therefore, it is possible to infer the identity, viability, and perhaps the potency of the unit within the cryobag from testing performed on these segments.

The volume required in this standard is based upon the assumption that this volume will be adequate starting material for the tests to be performed; however, this is dependent on the concentration of cells within the CB unit after collection and processing. The CBB must validate that the concentration of cells after using its collection and processing methods is sufficient for confirmatory typing and other tests that need to be performed on these samples. If it is not, the CBB may need to store a higher sample volume. Target means the goal; slightly less amount is acceptable if the CBB is still able to perform all of the testing.

The relationship between testing from segments and the results obtained from the CB unit should be determined.

Evidence:

The inspector must be provided with validation that the amount of cord blood in the sample is sufficient for the testing to be performed and that the sample cells are truly representative of the final product.

Example(s):

An example of validation could be measurement of the volume of each of the segments from a CB unit and performance of HLA typing, CD34, viability, etc. using cells from the attached segments.

STANDARD:

D4.1.1.1 The contents of each contiguous segment shall be representative of the CB unit.

Explanation:

The individual filling the bag must mix the CB unit well and fill both bag and segments simultaneously so that segments truly represent the contents of the bag.

STANDARD:

D4.1.1.2 When a CB unit is initially requested, a minimum of one (1) contiguous segment shall be used to verify the results of HLA typing.

Explanation:

Verification typing does not need to be performed with every request for a CB unit. HLA must be confirmed one time from an integral segment and the results made available in the information relayed to each Clinical Program interested in that unit.

Caution must be used when separating segments from the CB unit as welds may break in a manner that exposes blood to the storage environment. If that environment is liquid nitrogen, the entire inventory contained within that vessel may be at risk to undetected agents in the exposed unit.

Articles have been published to describe methods of determining identity (HLA) and evaluating potency or viability on the same segment, reserving remaining segments for future requirements or the Clinical Program. These tests can be performed on distinct segments on separate occasions, depending on the rationale for testing or the policy of the CBB.

STANDARD:

D4.1.1.3 When a CB unit is initially requested for clinical use, potency shall be tested in accordance with the Testing Requirements table in Appendix IV and shall meet the specifications outlined in the Specification Requirements table in Appendix V.

Explanation:

The use of an integrally attached segment for cell viability and potency analysis is recommended. In cases where segments are not available for this testing (e.g., if they have already been used for verification typing, cell counts are too low, etc.), a retention sample stored in a cryovial may be acceptable so long as it is representative of the CB unit.

Example(s):

Potency and viability analyses can be performed as directed by the CBB's policies, either for internal quality evaluations or at the time of initial or subsequent CB unit requests for as long as segments remain.

STANDARD:

D4.1.1.4 At the time of removal for testing, one (1) qualified person using a validated process or two (2) qualified people shall verify the identity of the segment.

D4.1.2 Additional samples of a minimum total of 2×10^6 nucleated cells divided into at least two (2) vials or additional contiguous segments.

D4.1.2.1 Representative and retention samples intended for viability or potency analysis shall be stored under the same conditions as the CB unit.

Explanation:

These samples are in addition to the integral segments required for CB unit identity and viability. Viable cell aliquots must be retained to permit testing of a unit's biological features, such as enzymatic activity when the unit will be used for transplantation in metabolic diseases.

Evidence:

The inspector needs to see validation of the testing performed in those samples to prove that the amount collected and stored in these additional samples is representative of the final product and tests performed using those samples is accurate and reliable.

STANDARD:

D4.1.2.2 Reference samples used for purposes other than viability or potency analysis shall be stored at -70°C or colder.

Explanation:

The requirement for storage of reference samples at -70°C or colder is intentionally conservative to provide the best samples for unanticipated tests in the future. Some infectious diseases already require storage at this temperature.

STANDARD:

D4.1.3 A minimum total volume of 3.6 mL of plasma from the CB unit divided into at least two (2) vials.

Explanation:

The rationale for volume requirements in a multiple of 1.8 mL is because standard vials are of this size.

STANDARD:

D4.1.3.1 The plasma shall be stored at -70°C or colder.

D4.1.4 Suitable material for preparation of at least 50 µg genomic DNA.

Explanation:

The primary purpose of this material is for HLA typing, but this is not the only test for which it can be used. Purity of the DNA is important and should be assessed.

STANDARD:

D4.2 At least one retention sample from the CB unit should be stored indefinitely.

Explanation:

Retention samples are useful for investigating adverse events or retroactive quality control activities. Indefinite storage does not mean that the sample must be stored forever; it means that no time limit for storage can be established. It is understood that once a retention sample is used for the purposes stated above that the sample will no longer be available.

Example(s):

In the U.S., the FDA requires storage of retention samples from unrelated CB units.

STANDARD:

D4.3 Maternal samples to be maintained shall include:

D4.3.1 From the birth mother, a minimum total volume of 3.6 mL of serum and/or plasma divided into at least two (2) vials.

D4.3.1.1 The serum or plasma shall be stored at -70°C or colder.

D4.3.2 From the genetic mother, suitable material for preparation of at least 50 µg of genomic DNA with the exception of egg or embryo donors.

Example(s):

Material suitable for preparation of genomic DNA may be purified DNA, frozen cellular material, or blots.

D5: CRYOPRESERVATION

STANDARD:

D5.1 CB units shall be cryopreserved using controlled rate freezing or an equivalent procedure validated to achieve adequate recovery, viability, potency, and stability.

D5.1.1 TNC recovery should be ≥ 60% after processing prior to cryopreservation.

Explanation:

The target of ≥ 60% is based on data received from many CBBs.

STANDARD:

D5.1.2 The duration from addition of cryoprotectant to initiation of freezing shall be minimized and validated by the CBB.

D5.1.3 The duration from completion of freezing to storage at -150°C or colder shall be minimized and validated by the CBB.

Explanation:

Validation must demonstrate a temperature cooling rate with acceptable endpoint temperatures and include cellular recovery, viability, and potency tests.

Validation studies should include the duration of cell exposure to the cryoprotectant prior to the initiation of cryopreservation while demonstrating cell viability and potency to length of exposure to the cryoprotectant. One can then determine how many CB units can be simultaneously processed within a timeframe that maintains acceptable cell viability. For CBBs that freeze multiple units at a time, studies should demonstrate consistency of addition of cryoprotectant and cryopreservation between various numbers of CB units so that processing staff know the limitations of their system.

Evidence:

CB cryopreservation temperature graphs demonstrate starting and endpoint temperatures. CB unit graphs should correspond to validated temperature graphs that have been approved by the CBB.

A CBB's policies should emphasize attempts to minimize the time between addition of cryoprotectant and initiating cryopreservation. This can also be included as a key element in staff training and evaluated at the time of competency assessment.

Example(s):

Although controlled rate freezing by use of a programmable device is the recommended method for cryopreserving CB units, alternative methods validated to protect cell viability may be used. Other methods of freezing (e.g., freezing in a mechanical freezer) can be acceptable with the appropriate level of vigilance:

- Ensure that canisters are separated, not stacked, to allow airflow around each unit.
- Limit access to the freezer during the freezing process so the temperature within the interior is not compromised.
- Trace the freezing kinetics via a data logger or other alternative tracing device to produce a cooling curve that demonstrates acceptable execution.
- Use methods demonstrated to result in acceptable post thaw viability and potency.

STANDARD:

D5.2 Cryopreservation Standard Operating Procedures shall specify that the following information is recorded for each CB unit:

D5.2.1 Total nucleated cell concentration within a defined range.

D5.2.2 The cryoprotectant, its final concentration, and the duration of cell exposure prior to freezing.

D5.2.3 Method of freezing and end-point temperature of cooling.

D5.2.4 Cooling rate and continuous monitoring of the temperature within a defined range.

D5.2.5 Freezing curve parameters within a defined range.

Evidence:

The inspector should review the SOP for acceptable cryopreservation parameters. The SOP should be detailed in the descriptions of the cryoprotectant used and the final concentration of both TNC and cryoprotectant.

STANDARD:

D5.3 CB units shall be stored in freezing bags designed and approved for the cryopreservation of human cells and shall be placed into individual metal canisters to provide protection during freezing, storage, transportation, and shipping.

Explanation:

The use of vials to provide long-term storage is not acceptable at this time. While it is possible that future innovation may modify this standard, the use of vials has a possibility to increase contamination, and may be difficult to prepare for infusion in the Clinical Program. CB units stored in vials prior to these Standards can still be used; however, the CBB should inform the Clinical Program so that the appropriate planning for transport, storage, and administration can take place.

Example(s):

Some suppliers have developed or are developing multi-compartment bags that can be used for regenerative medicine purposes. These Standards do not prohibit the use of such bags provided they are compliant with Applicable Law, are validated to maintain cell viability and potency despite differences in freezing kinetics, and are adequately labeled for each compartment.

STANDARD:

D5.3.1 Each freezing bag and tubing shall be examined visually for damage or possible contamination prior to use.

D5.3.2 Representative samples to be used for viability or potency assays shall be cryopreserved and stored under the same conditions as the CB unit.

D5.4 Processes must minimize the risk of overfilling and underfilling freezing bags.

D5.4.1 After filling, each freezing bag and segment shall be visually examined for possible leaking, overfilling or underfilling, and breakage of seals. The results of these inspections shall be documented.

Explanation:

Overfilling is defined as exceeding the manufacturer's volume recommendations. Underfilling can be equally detrimental to product safety as bags would be thinner, more brittle, and particularly susceptible to breakage. Exposure of product to nitrogen, whether liquid or vapor phase, is in itself a hazard because liquid nitrogen is not sterile. Aerosols are created in the vapor phase above the liquid when materials warmer than -196°C are introduced into the liquid. These issues have resulted in broken seals and bags that explode as the bag rapidly expands when exposed to warmer temperatures, even that of nitrogen vapor.

For CBBs that use overwraps, removal of excess air in the overwrap bag is extremely crucial. Temperature shifts can cause ballooning of the overwrap and eventually explosion and breakage.

Evidence:

The CB Processing Facility's policies should include guidelines to remove air and prevent overfilling or underfilling of the freezing bags.

The inspector should visually observe the filling and labeling process of the cryobag prior to cryopreservation.

D6: CONDITIONS FOR STORAGE

STANDARD:

D6.1 Storage devices containing CB units and samples shall be located in a secure area. The device or the area shall have locking capability that is used when the area is not occupied by the CBB staff at a minimum.

Explanation:

A secure environment is one where the general public or unauthorized persons do not have access, i.e., where opportunity for tampering with the CB units and their accessory components is reasonably minimized.

Example(s):

Examples of a physically secured area include: (1) key card access for persons authorized to have access to CB unit storage; (2) a physically locked area where authorized persons have keys, or (3) a method to provide security when staff are away from the work area (such as outside of business hours or during off-site duties).

STANDARD:

D6.2 Refrigerators and freezers used for the storage of CB units, blood components, human cells, tissues, specimens, or reagents used in CB unit collection, processing, or cryopreservation shall not be used for any other purpose.

D6.3 Procedures to minimize the risk of microbial cross-contamination of CB units shall be defined and maintained.

Explanation:

CB units, samples, and reagents should be stored in storage settings appropriate for the contents to maintain their integrity and potency and in an organized manner, with segregation, as appropriate. Storage controls should minimize risk of contamination between units that are in-process, units with identified risk, and those available for release. The process should be validated to be effective.

Evidence:

Records of CB unit storage must demonstrate use of quarantine as defined in storage SOPs.

Example(s):

There are several approaches that the CBB may choose to minimize the risk of cross-contamination. In addition to quarantine of all CB units until the CBB Director or designee and Quality Unit have approved the release of the CB unit, the CBB may overwrap the unit with a second plastic bag or store at-risk units in vapor phase liquid nitrogen.

STANDARD:

D6.4 Processes for storing CB units in quarantine shall be defined in Standard Operating Procedures.

D6.4.1 Quarantined CB units shall be easily distinguishable and stored in a manner that minimizes the risks of cross-contamination and inappropriate distribution.

D6.4.2 Each CB unit shall be maintained in quarantine storage until the CBB Director, or designee, and Quality Unit have approved the release from quarantine status.

D6.4.2.1 This review shall be based upon review of maternal communicable disease risk history, other medical history, maternal test results, and CB unit microbial culture results as required by Applicable Law.

Explanation:

Because results of all testing and screening of mothers and CB units are not completed prior to collection, quarantine is required until results are available and the CBB Director or designee and Quality Unit have approved the release of the unit from quarantine. This can occur after the completion of testing, confirmation of acceptable test results, and a review of maternal risk factors and family medical history. In settings where a unit with an identified infectious disease risk is not discarded, the unit should be stored in a manner to physically separate the unit from other inventory and should include segregation or designation in an automated electronic system.

Unrelated and related CB units may be placed in long-term storage together if a robust inventory management system is used that provides (1) appropriate segregation of inventory and methods to minimize cross-contamination and (2) systems to support identity and location of the CB unit. Inventory controls should support prevention of mix-ups and accidental release.

Evidence:

Each CBB must have an SOP to define storage areas and include processes and controls for quarantine and release, and also segregation, as applicable to the facility setting. Each record must be reviewed to confirm specified release criteria have been met prior to transfer or assignment of permanent status. In-process CB units, units with infectious disease risk, or units not acceptable for clinical use must be stored in a manner that distinguishes them from those acceptable for release in compliance with Applicable Law.

Example(s):

SOPs define the quarantine and release process and accommodate methods to maintain units with known infectious disease risk in a manner to prevent cross-contamination. Quarantine may be temporal, physical, electronic, or a designation within the CB unit record.

Some CBBs, particularly those using automated equipment or overwrap, store the CB unit in a permanent location directly after cryopreservation. In these cases, “release” may refer to the process of making a CB unit available for listing and distribution by assigning a permanent disposition status via hard copy or electronic documentation rather than physically relocating the CB unit.

When using physical quarantine methods, records of CB unit storage must clearly delineate storage locations for units as they move from quarantine and in-process locations to release to long-term storage locations, as defined in facility procedures. Physical quarantined storage can be achieved in a variety of ways:

- Storage in nitrogen vapor freezers eliminates contact through liquid nitrogen.
- Proper overwrap of CB units avoids contact even in liquid and can be an acceptable manner to quarantine units, including those positive for bacterial contamination. However, procedures must be in place for when the overwrap is violated. When segment removal violates the overwrap and:
 - the CB unit has no evidence of infectious disease risk through testing or screening, it is appropriate to store the CB unit with other units with no increased infectious disease risk, or
 - the CB unit has an identified infectious disease risk through donor testing or screening, excluding CMV, and is deemed acceptable for retention by the CBB Medical Director and Quality Unit, it must be placed in an appropriate quarantine method where it poses no contamination risk to other CB units.

STANDARD:

D6.4.3 Records shall indicate when a CB unit was released from quarantine into permanent storage.

Explanation:

Some CB units, such as those that are overwrapped, may already be physically located in their permanent storage assignment. Documentation of release must be available whether the CB unit is physically transferred or simply assigned a new disposition.

Evidence:

CBBs that quarantine CB units in vapor phase and subsequently transfer them into liquid nitrogen storage upon approval by the CBB Director or designee must document this activity in the CB unit record.

Records of CB unit storage must clearly delineate storage locations and designation for units as they move from quarantine and in-process locations to release to long-term storage locations, as defined in facility procedures.

STANDARD:

D6.4.4 CB units shall remain quarantined if the samples have reactive or positive screening test results for communicable disease or increased infectious disease risk obtained through the donor screening process.

Explanation:

When tests identify increased infectious disease risk, these CB units must be managed in a manner to limit risk of cross-contamination as noted above. Per the FDA, a donor whose specimen is reactive on a screening test for a communicable disease agent is considered at increased risk of infectious disease, regardless of the results of more specific or confirmation assays (except for a donor whose specimen tests reactive on a non-treponemal screening test and negative on a specific confirmatory assay and CMV testing). Increased infectious disease risk may also be identified through the donor medical history, physical exam, review of delivery records or other medical records, and also unit testing, as required by national competent authorities.

Evidence:

The CBB shall have an SOP defining storage controls used to separate and segregate units with increased risk of infectious disease through donor screening and testing or CB unit testing, including electronic designations, as applicable.

Review of records for CB units with increased infectious disease risk and those without such risk should show the appropriate storage locations and designations as defined in the facility SOP(s).

Example(s):

Examples of physical separation to limit risk of cross-contamination include the use of an overwrap or storage in vapor phase. Quarantined CB units should be segregated from units without identified risk, such as:

- overwrap,
- a separate storage device, or
- designation in an electronic system.

STANDARD:

D6.5 Temperature.

D6.5.1 CB units shall be stored at -150°C or colder.

D6.5.1.1 If CB units are not fully immersed in liquid nitrogen, the storage freezers shall be qualified to show that all CB units are maintained at appropriate temperatures.

D6.5.1.2 Transfer of cryopreserved CB units shall be validated and monitored.

Explanation:

The temperature of liquid nitrogen is -196°C; therefore, it is accepted that CB units stored in liquid nitrogen will be at this temperature. However, digital monitoring displays may not read this exactly but within a range around this temperature. The CB Processing Facility must establish a range of acceptable temperature readings.

If CB units are not fully immersed in liquid nitrogen, the storage system must be qualified to prevent unit storage above -150°C and include a continuous temperature monitoring system that records temperatures at least every four hours. For storage systems where units are fully immersed in liquid nitrogen, the storage system must provide levels adequate to maintain specified temperatures. At no

time should the facility's mechanism for long-term unit storage support storage at temperatures warmer than -150°C. Electronic monitoring systems for either temperature or liquid nitrogen levels should include alarm mechanisms that are tested periodically.

This requirement is based on evidence that long-term storage at warmer temperatures decreases potency. In addition, the warmer temperature of -135°C is closer to glass transition phase and provides less opportunity for CBBs to address facility or storage issues that could compromise CB unit integrity. The evolution in construction of vapor storage vessels is such that stability of the temperature within all sections of the storage area is more consistent than older vapor storage freezers. With this new design, more CBBs are choosing to store in vapor because this method achieves similar performance as liquid nitrogen storage without liquid nitrogen contact, further eliminating some of the risks of cross-contamination.

Evidence:

Records of continuous temperature monitoring devices must be available for review and include recording of temperatures every four hours at a minimum. Records for monitoring systems for liquid nitrogen levels demonstrate adequate levels, as defined by CB Processing Facility. Electronic alarm systems should include records of alarm testing.

STANDARD:

D6.5.2 Warming events at any time after cryopreservation shall be minimized.

D6.5.2.1 The duration of warming events shall be documented, and the impact on the CB unit shall be assessed.

D6.5.2.2 If a warming event may have decreased the potency of an unrelated CB unit, the unit shall not be made available for distribution for administration.

Explanation:

CB units must be maintained at the specified storage and transport temperatures. The CBB must have validated procedures to remove CB units and samples in a manner that protects cell viability. Deviations from these procedures must be documented in accordance with the QM Program.

Anytime that the temperature is above -150°C should be considered a potential warming event. Because unit volumes are small and are frozen in bags with large surface areas, their thermal kinetics are greatly affected by their environment. After cryopreservation, unit temperatures that transverse the glass phase will adversely impact the integrity of the cells. The CB Processing Facility must determine how its processes influence unit temperatures so it can be aware of the instances when glass phase is approached. For instance, validation may include mimicking the activity of retrieving a unit to secure a segment for confirmatory testing. Temperatures of units at the top and the bottom of the rack and time of exposures outside of liquid nitrogen would be tracked to determine the length of time it takes for each to approach -150°C. This validation includes temperature extremes such as exposure of a unit to ambient air and how long it takes to reach -150°C, and how temperatures are affected by vapor phase storage.

CB unit inventory must be managed in a way that minimizes variations in temperature. Opportunities for significant warming events occur when a unit is outside of its proper storage temperature for extended periods of time. Examples of these opportunities include:

- Transfer of CB units from a controlled rate freezing device to quarantine storage vessels,
- Transfer of CB units from quarantine to long-term storage,
- Removal of segments for confirmatory testing,
- Removal of a rack so that a segment can be removed from a CB unit that occupies the same rack,
- Storage of CB units in older vapor vessels that exhibit unstable temperatures when open.

The unit may potentially still be used, but it has to be assessed prior to making a decision to make it available for use. At the end of processing and all accumulated transfers, a CBB should be able to demonstrate that the process results in a viable CB unit.

Evidence:

Significant warming events do not necessarily occur every time the lid is opened, but these concepts must be addressed in CBB policies and avoided by staff during execution of activities that prolong exposure of CB units to temperatures warmer than -150°C. Temperature excursions should be avoided, but if they occur, a process to address the impact to affected units is required. Temperature excursions should be included as an aspect of stability programs, as described above.

Standard Operating Procedures define processes to limit unnecessary exposure to temperatures warmer than -150°C, including routine processes for CB unit transfer and segment removal. Validation testing records include facility-specific data to support acceptable unit viability for temperature excursions related to significant warming events. Procedures and records support the documentation of duration of warming events and the impact on the affected units.

Example(s):

To avoid opportunities for exposure of CB units to temperatures outside proper ranges, a CBB might recommend that transfer of units be performed in liquid nitrogen vapor, though this is not required.

STANDARD:

D6.6 There shall be a written stability program to assess cryopreserved CB units for post-thaw microbial contamination, potency, and integrity.

D6.6.1 A minimum of three (3) CB units per manufacturing method shall be assessed annually.

Explanation:

Because the length of CB unit storage is unknown, confidence needs to be demonstrated that the conditions of cryopreservation and storage result in units that can provide acceptable hematopoietic reconstitution. Since units cannot easily be tested prior to release, the CBB must develop a stability program that annually tests units of various storage duration for viability and potency. Applicable Law may specify what testing and the frequency of testing that need to be performed.

Processing methods change over time and may affect the expiration date. The stability program must test a reference sample from a CB unit from each method of processing used. When an expiration date has not been assigned, the unit should be assessed against available stability data prior to release for administration.

Stability testing may include:

- Integrity: Verify bag remains intact upon thaw,
- Sterility: Test CB unit for positive microbial cultures,
- Potency: Perform CBB-defined assays,
- Manufacturing processes: Evaluate methods for collection, processing, cryopreservation, storage temperature, and unit size.

Evidence:

The inspector will review the stability program and the associated policies and procedures for identifying CB units to be tested and the acceptable end-point parameters.

D7: MONITORING AND ALARM SYSTEMS

STANDARD:

D7.1 Refrigerators used for storage of CB units before cryopreservation shall have a validated system to monitor and record the temperature continuously or at a minimum every four (4) hours.

D7.2 Where CB units are not fully immersed in liquid nitrogen, freezers used for CB unit storage shall have a validated system to monitor the temperature continuously.

D7.2.1 The temperature shall be recorded every four (4) hours, at a minimum.

Evidence:

Validation and qualification records demonstrating that the systems in place are capable of monitoring storage temperatures continuously and recording those temperatures at a minimum of every four hours should be available for review by the inspector.

Electronic or hard copy records of ongoing temperature monitoring of refrigerators and freezers must be available.

Example(s):

Examples of temperature monitoring records may include but not be limited to:

- Temperature graphs – electronic or hard copy,
- Chart recorders,
- Direct observation readings.

STANDARD:

D7.3 *Where CB units are fully immersed in liquid nitrogen, there shall be a validated mechanism to consistently maintain levels of liquid nitrogen in liquid nitrogen freezers.*

Evidence:

For CB units stored fully immersed in liquid nitrogen, procedures detailing the system for maintenance of liquid nitrogen levels must be available. There must also be records that these levels were maintained throughout the period of product storage.

STANDARD:

D7.4 *Alarm Systems.*

D7.4.1 *Storage devices for CB units and samples shall have validated alarm systems that are continuously active.*

D7.4.2 *Alarm systems shall have audible and visible signals.*

D7.4.3 *Alarm systems shall be checked periodically for technical function. The records of such checks shall be maintained.*

D7.4.4 *The alarm system shall be capable of notifying designated personnel 24 hours a day.*

Explanation:

The designated personnel must be trained in handling the alarm and steps to take in the event that CB units must be salvaged. Notification should be designed in a cascade fashion, so that failure to notify the first designated person will trigger notification of a second one and so on. A sufficient number of persons should be designated so that the likelihood of failure of the entire cascade is reduced to a minimum. The cascade notification procedure should be periodically checked, preferably outside regular hours and in an unannounced way, to verify proper function and time required to notify one of the designated people.

Evidence:

Records of such checks demonstrating a sufficient notification procedure should be maintained.

STANDARD:

D7.4.5 *Alarm parameters shall be set to allow staff sufficient time to salvage CB units and samples.*

Explanation:

Alarms must not be set at the lowest possible temperature that CB units and samples can be stored without detriment to the biological materials. The temperature or liquid nitrogen level as indicated at which an alarm is set must allow staff time to correct the situation or transfer contents to alternative storage prior to putting products at risk.

STANDARD:

D7.4.6 Written instructions to be followed if the storage device fails shall be displayed in the immediate area of the storage device and at each remote alarm location.

Explanation:

Alarm parameters include lower and upper limits that would trigger the alarm. These limits should be outside the acceptable temperature ranges set by the CBB. This should allow time to address the freezer malfunction in time to prevent CB units from becoming unsuitable for administration due to warming events. It is understood that extenuating circumstances may prevent all CB units and samples from being salvaged, but the CBB must make reasonable attempts to devise a plan to salvage as many as possible.

The instructions must include a procedure for notifying designated staff and an outline of the procedures to follow to maintain the CB units at safe temperatures.

Evidence:

Alert and alarm levels should be defined within the relevant policy or operational procedure.

STANDARD:

D7.4.7 Any alarm event and its resolution shall be documented.

D7.5 Contingency plans or storage devices of appropriate temperature shall be available for maintaining CB units and samples at the storage temperature in the event the primary storage device fails.

Explanation:

In the event of primary storage device failure, there must be a procedure in place to maintain CB units at the specified storage temperature.

Example(s):

Steps to take until the device is fixed or replaced may include:

- Transfer CB units to back-up freezers,
- Transfer units to another facility,
- Place units in dry shippers,
- Manually top freezers with liquid nitrogen.

D8: DISPOSITION

STANDARD:

D8.1 The CBB shall have defined criteria for the disposition of a CB unit, including at a minimum:

D8.1.1 CB units released for listing on a registry.

- D8.1.2 *CB units released for clinical use.*
 - D8.1.3 *CB units released for research.*
 - D8.1.4 *CB units released for quality assurance activities.*
 - D8.1.5 *CB units that are discarded and persons authorized to approve discard.*
- D8.2 *CB units shall meet the requirements outlined in the Specification Requirements table in Appendix V.*

Explanation:

The CBB must have defined criteria for qualifying CB units for clinical use. This includes defining specifications for banking, listing on donor registry, and release for administration.

The CBB must also have a policy for qualifying CB units for research, quality assurance, and validation activities. This may include minimum acceptance criteria of CB units that will be selected for validation activities based on, but not limited to, pre-established test parameters, variables, and upper and lower limits included in the validation plan of the process intended to be validated. The CBB must have a policy for discarding CB units.

Separate requirements exist for unrelated and related CB units. For related CB units, if specifications are unmet, the CBB at a minimum must follow its processes for deviations and nonconforming units in the event the customer insists on storage.

Example(s):

The U.S. FDA Guidance Document, *“Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications”* lists required specifications for CB units to be licensed in Table A Required and Recommended Tests and Test Results (below). These criteria may also be useful for CBBs not necessarily requesting FDA licensure. This table is available at

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM187144.pdf>.

Table A Required and Recommended Tests and Test Results¹

From FDA Guidance Document, *Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications*

Product Characteristics ²	Testing	Sample (Type and Timing)	Results of Product Testing
Safety	Infectious diseases – Testing Required. (21 CFR 1271.45 through 1271.90)	Maternal peripheral blood obtained within 7 days of cord blood collection – Type and Timing Required. (21 CFR 1271.80(a) and (b))	All tests negative except non-treponemal test for syphilis when confirmatory test is negative. (Cytomegalovirus (CMV) results are recorded). CMV - Report
	Sterility – Bacterial and fungal cultures – Testing Required. (21 CFR 211.165(b), and 21 CFR 610.12)	HPC-C (pre-cryopreservation)*	No growth
	Hemoglobin	Cord blood** or appropriate donor sample obtained at time of cord blood recovery	No homozygous hemoglobinopathy
Purity and Potency ³	Total nucleated cells (TNC)	HPC-C (pre-cryopreservation)	$\geq 5.0 \times 10^8$ TNC*** /unit HPC-C
	Viable nucleated cells	HPC-C (pre-cryopreservation)	$\geq 85\%$ viable nucleated cells
	Viable CD34+ cells (flow cytometry)	HPC-C (pre-cryopreservation)	$\geq 1.25 \times 10^6$ viable CD34+ cells**** /unit HPC-C
Identity	Human leukocyte antigen (HLA) Typing	Cord blood	Report
	Confirmatory HLA typing	Attached segment of HPC-C	Confirms initial typing
	Blood Group and Rh Type	Cord blood	Report

¹ Testing Sample (Type and Timing), and Results are recommended unless specifically noted as required.

² The PHS Act requires a demonstration that the product is safe, pure, and potent.

³ Other purity and potency assays may be considered under the BLA.

* Sample may be obtained before or after addition of the cryoprotectant.

** Cord blood = a sample of unmanipulated cord blood. A red cell sample or other cord blood aliquot obtained after volume reduction may be used for testing with appropriately validated reagents or test systems.

***Based on 20 kg recipient, a target dose of $\geq 2.5 \times 10^7$ nucleated cells/kg and $\geq 70\%$ post-thaw recover = 1.7×10^7 nucleated cells/kg.

****Based on CD34+ cells $\geq 0.25\%$ of TNC prior to freezing.

STANDARD:

D8.3 *Nonconforming CB units.*

D8.3.1 *The CBB shall have a policy for the management of CB units that are not accepted into inventory.*

D8.3.2 *The CBB shall have a written policy for the management of CB units that do not meet in-process or final endpoints and/or specifications.*

D8.3.3 *The CBB shall have a written policy to address positive or indeterminate results found during the screening process and/or laboratory testing of samples.*

Explanation:

Nonconforming CB units do not necessarily have to be discarded. There are uses for units for reasons other than clinical administration. For public banking, CBBs will be required to adhere to all regulatory requirements regarding inclusion/exclusion criteria as outlined by applicable regulatory agencies. Since related banking is a contractual service, the private CBBs may be more tolerant of acceptance issues than a public CBB. For example, a cryopreserved TNC count may have a lower threshold at a related bank than what is acceptable at a public bank. These criteria should be well documented and explained to the prospective cord blood donor. Issues related to incorrect labeling or inappropriate labeling that make unit identity questionable should be an exclusion criterion at all banks.

If a CBB elects to retain a nonconforming CB unit, it must clearly distinguish the unit from the general inventory.

Example(s):

Alternative uses for nonconforming uses include research and quality control.

Additionally, some CBBs may establish separate programs for underserved minority populations for which CB units typically do not meet specifications, such as the minimum acceptable TNC count. For such programs, there must be clearly written policies about how the bank incorporates its exceptional release process for these nonconforming units. There should be a system in place to alert bank personnel of nonconformances.

STANDARD:

D8.4 *Disposal.*

D8.4.1 *The records for discarded CB units shall indicate the unique numeric or alphanumeric identifier of the CB unit; the reason, date, and method of disposal; and the individual who disposed of the CB unit.*

D8.4.2 *If processing is initiated before obtaining a signed consent, the CB unit shall be clearly identified and distinguished from consented CB units during all processing stages.*

D8.4.2.1 *Unrelated CB units lacking signed consent shall not be cryopreserved and shall be discarded.*

D8.4.2.2 *Cryopreserved related CB units lacking a signed consent shall be maintained in quarantine status until consent has been obtained.*

Explanation:

The disposition of a CB unit impacts the level of oversight necessary for unit disposal. Some CBB models necessitate the initiation of processing before the signed consent is received by the CB Processing Facility to preserve the cells. In these cases, the CB unit must be clearly identified and distinguished from other CB units. The facility must receive the consent for an unrelated unit before processing is completed (considered to be at the time of cryopreservation). If not received, the unit must be discarded.

STANDARD:

D8.4.3 *For related CB unit disposal:*

D8.4.3.1 *Disposal shall comply with the terms of disposal in the written agreement.*

Explanation:

Disposal of related CB units must be highlighted in the informed consent or documented in the agreement with the family. This discussion must include the facility's policies for disposal and the family's options for alternative storage. An example of issues is whether the unit must be transferred to a CBB for continued related banking or if the unit can be crossed over to an inventory for research or unrelated allogeneic use. If a unit is to be crossed over, the unit must have met all unrelated allogeneic requirements at the time of collection and processing. Other issues include transportation, financial responsibilities, and who is responsible for arranging the alternate storage.

If the CB unit is donated for research, the CBB should document the identity of the institution in receipt of the unit, the transfer agreement, and institutional approval for the specific research being conducted. The maternal donor must clearly give her consent if the unit is to be used for research. If the unit is sold for commercial use, this also must be disclosed to the mother.

Evidence:

A copy of the informed consent or written agreement should be included with the disposal documents.

Example(s):

Approaches to dealing with related disposal include:

- Contacting the CB unit donor or prospective recipient, if alive,
- Obtaining informed consent from the biological mother or legal guardian in accordance with Applicable Law in the case of a minor donor or prospective recipient,
- Contacting the family member with whom the original contract/consent to collect and store the CB unit was made, or designee,
- Transferring the CB unit to another facility if consent to dispose is denied.

The discussion regarding disposal may also occur in consultation with the prospective recipient's physician.

In the instance where there is no longer a family need for a CB unit that otherwise meets unrelated allogeneic CB banking criteria, the family may be offered the opportunity to release the product into a CBB's unrelated allogeneic inventory. This consent for release must be documented and must follow Applicable Law.

Disposal of a CB unit accepted into inventory may require approval from key personnel, whereas a CBB may choose to allow processing personnel to discard units that do not meet volume thresholds.

STANDARD:

D8.4.3.2 Reasons for disposal and notification of the donor's family shall be documented.

Example(s):

Rationale for discarding a CB unit may be related to the following:

- Delivery issues/complications,
- Inappropriate donor screening results (risk factors, family health history, etc.),
- Compromised collection bag integrity,
- Incomplete or inappropriate labeling,
- Positive infectious disease testing,
- Unacceptable quality control indexes,
- Processing issues,
- Low TNC count or volume.

D9: CORD BLOOD UNIT TESTING

STANDARD:

D9.1 The CBB shall define tests and procedures to determine CB unit safety, viability, potency, and integrity and to document that CB units meet predetermined release specifications as outlined in the Specification Requirements table in Appendix V.

D9.1.1 Records of all such test results and procedures shall become part of the permanent record of the CB unit.

D9.1.2 The CBB shall retain records for each test methodology used for CB units that have been banked. These methodologies must be traceable to individual CB units.

Explanation:

Test methodologies including reagent manufacturer, lot numbers, and expiration dates must be maintained and shall become part of the permanent records.

STANDARD:

D9.2 Testing procedures shall include:

- D9.2.1 *The use of established and validated assays, equipment, and test procedures for the evaluation of the CB unit.*
- D9.2.2 *Adequate provisions for monitoring the reliability, accuracy, precision, and performance of test procedures and instruments.*
- D9.2.3 *Adequate identification and handling of all samples so that they are accurately related to the specific CB unit being tested, to its infant donor, to the maternal donor, and to the specific recipient, as applicable.*
- D9.2.4 *Verification of new reagent lots to provide comparable results between lots or give results in agreement with suitable reference ranges before or with placement into service.*
- D9.2.5 *Where available, use of reference or quality control material demonstrated to give results within the defined range established for that material.*
- D9.2.6 *Functional checks performed for testing instruments, as appropriate, prior to testing of CB units.*
- D9.2.7 *Documentation of ongoing proficiency testing as designated by the CB Processing Facility Director. The results shall be reviewed by the CB Processing Facility Director or designee and outcomes reviewed with the staff and Quality Unit, if applicable.*

Explanation:

CB Processing Facility controls are processes that support processing and characterization of CB units. They are to be scientifically sound, i.e., based on logical, validated, and referenced practices.

Functional checks may include daily quality control, calibration, or preventive maintenance.

Example(s):

It is recommended that viability and potency should be demonstrated after cryopreservation and storage to confirm the integrity of the CB unit. Caution must be used in interpreting traditional viability tests; however, because their accuracy is limited by the stage of cellular repair after thaw.

STANDARD:

D9.3 *CB units shall be tested as outlined in the Testing Requirements table in Appendix IV.*

Explanation:

Appendix IV outlines the tests that are required, including when the tests must be performed and on what sample. Specific requirements for some individual tests are specified later in this section.

The nucleated red blood cell count (NRBC) must be reported. However, a CB unit that was processed prior to this requirement may not have an enumerated population of cells. Rubinstein, et al, reported that NRBC dose predicted speed of engraftment; therefore, inclusion of NRBCs in the Total Nucleated Cell (TNC) count does not reduce the effectiveness of the post processing TNC count as an index of the quality of a unit as a graft. The correlation between the number of NRBCs and the number of HPC probably reflects the involvement of early stem cells in erythroid responses (Blood. 2002 Oct 1; 100(7):2662-4). However, the CBB must clarify the contribution of NRBC to the nucleated cell population for the Clinical Program to facilitate an informed donor selection. Additional parameters of the blood count should be reviewed to exclude congenital neutropenia, thrombocytopenia, and immune deficiency.

ABO/Rh typing provides important information to the Clinical Program with regard to blood product support of a recipient post-transplant. This typing also affords a means of CB unit identification both in the CBB and at the Clinical Program.

Because societies are becoming more integrated and abnormal red blood cell diseases are carried by populations previously considered unable to transfer or be affected by them, hemoglobinopathy testing must be performed for unrelated CB units regardless of the family's ethnic background or history. The screening test must utilize a method that distinguishes hemoglobin A, A2, S, C disease or trait. Testing for alpha and beta thalassemia is recommended if indicated. CB units homozygous for either sickle cell disease or thalassemia will be deferred. CB units heterozygous for either sickle cell trait or thalassemia will be accepted and distinguished as such; CB units heterozygous for both sickle cell and thalassemia will be deferred. Testing may either be performed on residual red blood cell material remaining post-processing or on a sample of whole CB prior to processing. In private CB banking, relationship with the donor is maintained. Testing of the donor for hemoglobinopathies can be performed at the time that the unit is under evaluation for use by a treating physician. Additionally, hemoglobinopathy testing is capable of being performed on the unit prior to release since unit testing results do not need to be provided on a registry. Newborn screening is also acceptable. A positive test is defined as the presence of a homozygous hemoglobinopathy, e.g. Hgb SS (SA in fetus), or double trait on the same gene (e.g. SC or Sbeta thal). The presence of a single trait is not an exclusion. The presence of two traits on different genes (e.g. alpha thal trait and beta thal trait) is not necessarily an exclusion and should be evaluated by the CBB Medical Director.

Though testing based on intact cell membranes and active cell metabolisms that exclude Propidium Iodide (PI), 7-Amino-Actinomycin D (7-AAD), or trypan blue dyes are commonly used to assess viability, CFUs are grown from functionally viable cells and increase confidence in CB unit quality and ability to engraft. The term "CFU" is used generically and the CBB may choose to test for total CFU or CFU-GM. If the CBB only performs GM assays, this must be communicated to the Clinical Program. A CBB may use an alternative potency assay if it is validated at the bank.

Infectious disease testing of the maternal samples is understood to be a surrogate test, and strongly reflective of the infectious status of the CB unit since the circulation is shared during gestation. Infectious disease testing is performed on a maternal sample collected within seven days before or after delivery, generally with results available prior to release to inventory.

Evidence:

Results of infectious disease tests are part of the CB unit record and are reported to the Clinical Program. Although it is not necessary to identify the particular test in the unit record, CBB documents should be

able to trace the method and even the version or generation of the test used for testing. When used for testing reference samples, CB Processing Facilities in the U.S. should indicate that results were obtained from tests not yet approved by the FDA for these purposes.

Example(s):

Unless otherwise specified in Appendix IV or in the Standards, the testing can be performed anytime as long as it meets the minimum requirements in the table. For example, microbial cultures must be performed between end of processing and cryopreservation, but ABO/Rh testing can be performed any time before listing the CB unit, even at the time of collection.

The U.S. FDA published draft guidance on potency testing in October 2008 titled, "Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products." This guidance can be found on the FDA website at:

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072571.htm>. Typically, laboratories use methylcellulose media to discriminate all colony types but it is acceptable to assess GM or any other validated method whose ranges are described in the facility's policies and procedures.

If required, CB unit infectious disease testing can be performed at the same time or can be deferred until the CB unit is requested for transplant. Alternatively, samples retained by the CBB can be transferred to the Clinical Program for testing in its own facility.

Testing maternal donors for CMV is required; however, testing the CB unit for CMV is optional. Transplant patients typically receive many blood products in support of their therapies and exposure to CMV is related to the frequency of transfusion. There are a variety of ways that CBBs address testing for CMV. Often, CMV is included in the infectious disease panel offered by the CBB's infection disease testing laboratory. Total antibody including IgG and IgM can be tested on maternal samples, and CB samples may be tested for IgM when maternal samples are positive. CMV PCR is available in some labs.

In the U.S., state and reference laboratories have standards for hemoglobinopathy testing. Diagnostic tests including HPLC, isoelectric focusing, or electrophoresis are appropriate, while SICKLEDEX or rapid testing assays such as those used in Transfusion Medicine laboratories are not. The CB Processing Facility Director must confirm that procedures used are appropriate.

Infectious disease testing of the CB unit is recommended by these Standards though it is understood that many kits are not FDA-approved for this specimen. Clinical Programs in the U.S. are interested in their liability regarding use of CB units. If testing is performed but not FDA approved, a CBB can report results with notation that this assay is not yet approved in these circumstances by the FDA. For more information regarding donor eligibility determinations based on donor screening and testing for relevant communicable disease agents and diseases (RCDADs), refer to the FDA's Guidance for Industry for Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) at

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM091345.pdf>.

For a list of FDA approved donor screening tests, refer to

<http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/TissueSafety/ucm095440.htm>.

CB unit infectious disease testing is required by the European Health Ministry and must be performed prior to importing a product to a European country, either by the CBB or by submitting samples to the Clinical Program. CBBs should submit a list of locally required tests and the menu of infectious disease tests performed by their laboratory in the application process. Inspectors must note if the CBB is following its specific national requirements.

STANDARD:

D9.3.1 CBC with differential testing shall include enumeration of neutrophils, lymphocytes, monocytes, and platelets. Parameters for neutrophils, lymphocytes, and platelets shall be defined.

Explanation:

A differential is obtained to screen for the presence of inherited blood dyscrasias.

Example(s):

Congenital *neutropenia* (Kostmanns Syndrome) would be suspected if the neutrophil count was low (e.g. <10%) or the absolute neutrophil count was calculated to be below 1,500/uL (% neutrophils + % bands x total WBC/uL). A screen for *lymphopenia*, which could be a sign of severe combined immunodeficiency syndrome or another inherited complex immunodeficiency syndrome, should be conducted. The absolute lymphocyte count should be 1,500/uL or greater (% lymphs x WBC/uL). In the absence of neutrophils or lymphocytes or with maternal cell engraftment, *eosinophilia* may be prominent. If eosinophilia (>10%) is present, an investigation should occur. Extreme *anemia*, in the absence of known bleeding, is also a potential sign of a congenital red cell dyscrasia. Pure red cell aplasia (Diamond-Blackfan Anemia) and alpha thalassemia can both present in the newborn period. In the case of DBA, the MCV will be very high, while in the case of alpha thalassemia, the MCV will be very low (<90). *Thrombocytopenia* (platelets <100K/uL) may be a sign of congenital thrombocytopenia (megakaryocytic thrombocytopenia, thrombocytopenia with absent radius, fanconi anemia). Since variable amount of anticoagulant may be added by different CBBs in a CB product, the dilution factor needs to be taken into account in order to determine accurate range of differential counts.

If any of these abnormalities are present, further investigation should occur. If investigation is not possible, the CB unit should not be listed on a donor registry or made available for administration. In some cases, notification of the baby's physician could help identify a baby at risk for the clinical problems associated with these inherited diseases.

STANDARD:

D9.3.2 Microbial cultures shall be performed using a system validated for the growth of aerobic and anaerobic bacteria and fungi.

D9.3.2.1 CB units for unrelated use shall be free from microbial contamination.

Explanation:

The nature of the delivery process suggests that a level of culture positivity can be expected. The CB Processing Facility should establish acceptable positivity rates to determine when internal thresholds have been exceeded and when action should be taken.

Microbial cultures must be obtained from a sample representative of the final CB unit after processing. The CBB must validate bacteriological cultures.

Example(s):

The cultures of each can either be obtained together after processing or be obtained separately via the CBB's process of qualifying the cryopreservation media. Culture inoculum may be obtained from:

- Post-processing byproduct where manufacturer volume recommendations can be fulfilled,
- Final product prior to cryopreservation with cryoprotectant,
- Final product prior to cryopreservation without cryoprotectant,
- Cryoprotectant material(s) as additional safeguards relating to reagent sterility:
 - Single use vials, or
 - Tested multi-use vials.

Validation of a CBB's method of detecting microbial contamination can be achieved by equivalency studies, serial dilutions, or reference to published sources in accordance with Applicable Law.

STANDARD:

D9.3.2.2 For related CB units, the results of positive microbial tests shall include identity and sensitivities of the organism(s). These results shall be reported to the prospective Clinical Program.

Explanation:

Unrelated CBBs do not list, or make available, CB units that have demonstrated microbial growth; in related programs, culture-positive units may be retained. Unrelated CB inventories established prior to these Standards may have retained units demonstrating bacterial growth. These units should be quarantined in order to reduce the risk of contamination to other stored CB. If a culture-positive product is distributed, the CBB must disclose the sensitivities to the Clinical Program.

The identification of organisms and sensitivity must be determined at the time they were first detected. Antimicrobial sensitivities refer to aerobic bacteria, anaerobic bacteria, and fungi. In the related banking setting, the CBB Medical Director need not authorize CB units for release unless considered for use in administration. A positive microbial test may not preclude a related unit from being infused, so long as the transplant physician and recipient are informed. However, the CBB Medical Director must still review unit parameters before releasing the unit according to pre-determined criteria, whether internal or as defined by the transplant physician.

Example(s):

The cultures of each can either be obtained together after processing or be obtained separately via the CBB's process of qualifying the cryopreservation media. Culture inoculum may be obtained from:

- Post-processing byproduct where manufacturer volume recommendations can be fulfilled,
- Final product prior to cryopreservation with cryoprotectant,
- Final product prior to cryopreservation without cryoprotectant,
- Cryoprotectant material(s) as additional safeguards relating to reagent sterility:
 - Single use vials,
 - Tested multi-use vials.

Validation of a CBB's method of detecting microbial contamination can be achieved by equivalency studies, serial dilutions, or reference to published sources in accordance with Applicable Law.

STANDARD:

D9.3.3 HLA Class I and Class II typing shall be performed by DNA-based methods.

Explanation:

If a CB unit is stored for related use and not tested upon storage, HLA typing must be determined and compared with donor typing prior to release. Before listing an unrelated unit, typing must include a minimum of first "field" typing (low resolution, e.g., A*01) for HLA-A, B, and DRB1, which must be included when listing a unit. A minimum of one "field" from DNA-based HLA typing is required to list a unit for search.

The rationale for allowing only low resolution or one "field" at the time of listing is because this approach is sometimes used as a cost-control issue. However, to help ensure the appropriate selection of a CB unit, the CBB must perform high resolution typing (two "fields") for HLA-A, B, C, and DRB1 before actually releasing a unit for administration.

Example(s):

Though not required, it is highly recommended that high resolution typing is performed prior to listing the CB unit in order to provide Clinical Programs with enough information to make a selection in minimal time.

STANDARD:

D9.4 Test results that are positive or outside of the established range and are relevant to the infant donor's health shall be communicated to the infant donor's mother or legal guardian and/or her physician according to Applicable Law and CBB policies and Standard Operating Procedures.

D10: MATERNAL TESTING

STANDARD:

D10.1 The maternal blood sample obtained within seven (7) days before or after collection of the CB unit shall be tested for evidence of infection as outlined in the Testing Requirements table in Appendix IV, utilizing assays required for volunteer tissue donations and according to Applicable Law.

Explanation:

Maternal serologic and NAT testing is an appropriate surrogate for representing the infectious status of the CB unit for a number of reasons. While admittedly conservative, this approach enhances protection of unit inventories and recipients. The placenta is an effective barrier for disease agents but the extent of vertical transmission is not completely consistent. Furthermore, reference samples may be inadequate due to dilution with anticoagulant and processing reagents. Many infectious disease testing technologies have not been approved for CB specimens in various countries.

Infectious disease panels may change due to emerging pathogens. It is expected that CBBs include detection of agents based on significance for their location and donor population. Other communicable disease tests should be added to the donor evaluation as they become available and recommended to increase CB unit safety. Testing for additional infectious agents may be included by governmental regulation as they become a global or community health care issue.

West Nile Virus transmission from infected donors has been confirmed in recipients of blood components and solid organs. This transmission has resulted in subsequent infection and death of the recipient. Testing results may influence the timing of recipient conditioning or lead to selection of an alternative cell source when possible.

Transfusion of blood components or infusion of crystalloid solutions, or both in significant amounts can dilute plasma. As required by Applicable Law, systems should be in place to prevent the collection of samples from maternal donors for infectious disease testing if a significant volume of blood or other fluid was infused. If the assessment wasn't made in advance, it must be made within the time frame that allows the CBB to obtain a repeat sample within seven (7) days of collection. There must be documentation that this has been assessed.

When required, CBBs must report positive results within the specified timeframes per Applicable Law.

Evidence:

SOPs must define processes for performing testing within validated timeframes and testing methods per Applicable Law and policies of the CBB. Document reviews of CB unit and testing records should support compliance with these requirements.

Example(s):

This standard defines the minimum requirements for infectious disease screening. For CB units in the U.S, laboratories must use approved, cleared, or licensed donor screening tests for tissue donors, according to manufacturers' instructions. Testing must be performed in labs certified to perform these tests under CLIA or equivalent requirements as determined by CMS. Similarly, in other countries, the testing and laboratory requirements are specified by the national competent authority. For EU member states, the tests must be carried out by a qualified laboratory, authorized as a testing center by the competent authority in the Member State, using CE-marked testing kits where appropriate. The type of test used must be validated for the purpose in accordance with current scientific knowledge.

CMV testing may be required by national competent authorities. In the U.S., CMV total antibody testing is required on a maternal sample, using an FDA-licensed, approved donor screening test.

The CBB may need to conduct more than one test in order to adequately and appropriately detect a single communicable disease agent or disease, as defined by Applicable Law. (For example, at the time of revision of these standards, FDA requires testing using donor screening test kits in a CLIA lab for HIV-1 and HIV-2 antibodies and HIV-1 NAT testing, and also antibodies to HIV-1, Group O, unless HIV-1, Group O donor risk is appropriately evaluated during donor screening. In addition, other testing for infectious transmissible agents may be required by Applicable Law or implemented per institutional policy. Similarly, EU member states may amend or introduce additional testing requirements. (For example, per EU requirements, testing donors for antibody to Human T-cell lymphotropic virus, type I is required only for donors at risk. Additionally, testing strategies may include repeat serological testing after 180 days, NAT testing, testing of a sample of cord blood, or other testing requirements as defined by National Competent Authority.)

According to the FDA, relevant communicable disease agents and diseases (RCDADs) may be assessed through donor screening and/or donor testing. FDA intends to notify the industry through published guidance from time to time of any additional relevant communicable diseases and include methods (screening and/or testing) by which those agents should be assessed. 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 of the disease or disease agent.
- It is sufficiently prevalent as to affect the potential donor population.
- There could be fatal or life-threatening consequences as a result of transmission.
- Effective screening mechanisms and/or an approved screening test for donor specimens have been developed.

The U.S. FDA guidance document, titled “Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps),” describes algorithms for determining if plasma dilution is sufficient enough to affect test results. This guidance is available at <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm091345.pdf>. For example, the guidance states that for donors over 12 years of age, more than 2000 milliliters of crystalloids within one hour immediately preceding the collection of samples is believed to be sufficient to affect the results of communicable disease agent testing. Based on this information, a CBB could specify in SOPs that samples should not be drawn if the maternal donor has received two or more liters of intravenous fluids in the previous hour.

STANDARD:

D10.2 Positive or indeterminate test results, excluding cytomegalovirus, shall be communicated to the maternal donor and/or her physician according to Applicable Law and CBB policies and Standard Operating Procedures.

Explanation:

Maternal testing specimens are required to be drawn within seven days before or after delivery to reflect the infectious status at the time of collection of the CB unit. Abnormal results are communicated to the maternal donor, her physician, or both so that appropriate follow up can occur.

The rationale for reporting indeterminate results is to alert physicians and mothers of potential health related issues. Reporting to public health authorities is not necessary if confirmatory tests are negative.

Some abnormal testing results may be urgent and require the CBB to notify the donor or the donor's physician to protect the health of the mother or infant donor. The CBB must comply with Applicable Law for donor notifications and timeframes based on requirements for various communicable diseases and disease agents.

Evidence:

The CBB must have defined parameters within their procedures that specify when to quarantine or discard these CB units and how abnormal test results are managed with regard to donor, physician, and public health notification. Records for abnormal test results, when traced to the mother and unit, demonstrate compliance with SOPs for disposition and management of the unit and notification of the donor, physician, and authorities per facility policy and Applicable Law. Records should document that donors were tested for these infectious agents within the specified time period and that the results were obtained and reviewed by CBB Medical Director or designee prior to the release of the unit.

Example(s):

An example of a potentially urgent finding could be a positive HIV test where immediately counseling a breast-feeding mother would be appropriate.

STANDARD:

D10.3 All maternal samples should have negative or non-reactive test results with the exception of Cytomegalovirus antibody, Hepatitis B core antibody, and non-treponemal-specific syphilis testing.

Explanation:

The tests included in this standard can be positive or reactive as long as certain requirements are met; however, the CBB has the responsibility to confirm such exceptions are allowed by the Applicable Law and registries through which it lists unrelated CB units. Some registries may not allow exceptions.

Evidence:

Consistent with Applicable Law, SOPs define what, if any, reactive donor screening test results are acceptable for storage and release of a CB unit for administration. (This is supported by the method and documentation required for such release.) Unit records must illustrate compliance with Applicable Law and facility policy for reactive test results.

Example(s):

If allowed by Applicable Law, many institutions may allow the use of CB units that are reactive/positive for anti-HBc, provided there is no other testing suggestive of Hepatitis B infection. SOPs should address disposition of units with reactive donor screening test results and include specifics for use of units with any reactive testing. Unit records should appropriately show disposal or non-clinical use for all results other than those allowed as exceptions and appropriate quarantine policies, consistent with facility-specific policy and Applicable Law.

STANDARD:

D10.3.1 If allowed by Applicable Law, maternal samples that are Hepatitis B core antibody positive and are accepted shall be HBV negative by DNA testing and Hepatitis B Surface Antigen (HBsAg) nonreactive/negative.

Explanation:

In some countries, maternal samples that are hepatitis B core antibody positive may be accepted if they are hepatitis B negative by DNA testing. This standard applies to this situation where allowed by Applicable Law for CBBs that wish to salvage CB units that are hepatitis B core antibody positive. CBBs are not required to test for hepatitis B by DNA testing; they may reject all units that are hepatitis B core antibody positive rather than proceed to DNA testing. Although these standards allow for the retention of hepatitis B core antibody positive units when hepatitis B by DNA testing is negative, these abnormal testing results must be explicitly communicated to the Clinical Program prior to release.

STANDARD:

D10.3.2 If allowed by Applicable Law, maternal samples that test positive for syphilis using a non-treponemal-specific screening test and are accepted shall be negative using a treponemal-specific confirmatory test.

Explanation:

Non-specific syphilis donor screening testing such as RPR or VDRL testing may be associated with higher false reactive rates than those donor screening tests that are specific for *treponema palidum*. For example, as an exception, FDA allows a donor to be determined as eligible if an FDA-approved non-treponemal donor screening test is positive or reactive and a specific treponemal confirmatory assay (FTA-ABS) is negative, provided all other required testing and screening is negative/nonreactive.

Evidence:

With regard to syphilis testing, if CB units are retained for possible infusion, SOPs must be detailed enough to distinguish practices for treponemal versus non-treponemal donor screening testing and confirmatory assays so that policies can be evaluated against requirements of Applicable Law.

Example(s):

In the U.S., if a treponemal-specific screening test or a specific treponemal confirmatory test is positive, the CB unit cannot be labeled as eligible and the units must remain in quarantine storage.

STANDARD:

D10.4 If Applicable Law and CBB policies and Standard Operating Procedures allow release of CB units from quarantine where the maternal samples are positive/reactive for Hepatitis B core antibody or non-treponemal syphilis, the CBB must have a written procedure that describes the documented notification of relevant results to the Clinical Program prior to release for administration.

This page intentionally left blank.

CORD BLOOD LISTING, SEARCH, SELECTION, RESERVATION, RELEASE, AND DISTRIBUTION STANDARDS

Part E

- E1 General Requirements
- E2 Review of Cord Blood Unit Records
- E3 Cord Blood Unit Selection and Release for Administration
- E4 Cord Blood Unit Distribution to a Clinical Program
- E5 Transportation and Shipping of Cryopreserved Cord Blood Units
- E6 Transportation and Shipping Records Requirements
- E7 Clinical Outcome Data

PART E: CORD BLOOD LISTING, SEARCH, SELECTION, RESERVATION, RELEASE, AND DISTRIBUTION STANDARDS

E1: GENERAL REQUIREMENTS

STANDARD:

- E1.1 There shall be designated facilities with defined areas for CB unit listing, search, selection, reservation, release, and distribution to prevent mix-ups, mislabeling, or other errors.*
- E1.2 The CBB shall have policies and Standard Operating Procedures for the following at a minimum:*
- E1.2.1 Selection, reservation, release, and distribution of CB units to Clinical Programs.*
 - E1.2.2 For unrelated use, listing and search of the CB units.*

Explanation:

Prior to a CB unit being made available for search and subsequent administration, it must undergo a documented review of all aspects of the collection, processing, cryopreservation, storage, and testing in order to ensure the CB unit is of an acceptable quality, is safe for transplantation and maintains potency. The acceptance criteria for this qualification (which in most circumstances would be performed prior to both listing for search and again prior to release for administration) must be clearly documented with the CBB's SOP.

In addition to defining quality parameters such as both pre- and post-cryopreservation cell counts, viability, the results of infectious disease marker screening and testing and microbial testing, and a review of the maternal and family medical history, the CBB should describe its qualification review practice within its SOPs. This should include identifying personnel with expertise to understand the technical aspects of the processing procedure, critical review of the freezing curve, and a determination that the endpoints of processing have met established criteria.

Evidence:

CBBs should be able to provide evidence that this review or qualification process is performed prior to listing in a registry database (making the unit available for search) and again before release of the CB unit for administration.

Examples:

In addition to the SOP, CBBs may develop a checklist(s) that includes those criteria against which each CB unit is reviewed in order to determine its suitability for listing or release.

STANDARD:

- E1.2.3 For allogeneic use, verification of HLA typing of the CB unit.*
- E1.2.4 For allogeneic use, verification that the infant donor and the recipient are different individuals in the case of a complete HLA match.*
- E1.2.5 For autologous use, verification that the CB unit, the infant donor, and the recipient are the same individual.*

- E1.3 *There shall be a Standard Operating Procedure that defines a process to prevent listing of related CB units for unrelated use.*
- E1.4 *If the CBB utilizes a registry, the CBB shall use a validated process for uploading CB unit information to the registry.*

Explanation:

Registries include listing organizations and entities that perform search and match functions.

STANDARD:

- E1.5 *The CBB or registry shall have a validated electronic record system that enables search and match operations and reporting of results within a defined timeframe.*
- E1.5.1 *If an outside agency is used for search and match functions, its electronic record system shall meet these Standards.*
- E1.6 *The CBB or registry shall have policies and Standard Operating Procedures for the reservation and allocation of CB units.*
- E1.6.1 *There shall be a system to prevent simultaneous reservation of a CB unit for more than one potential recipient or for more than one potential Clinical Program.*
- E1.6.2 *At the time a CB unit is removed from inventory, the CBB shall notify all registries on which the CB unit is listed that it is no longer available.*

Explanation:

If multiple registries are populated by the CBB inventory data or if the CBB performs internal searches, there must be systems in place to confirm that CB units are appropriately removed from inventory at the time of reservation or release. It is important that the reservation system have the capability to remove units from searches or identify them as unavailable for administration if they are being evaluated or used for another patient.

If a potential recipient has sought evaluation and medical advice from multiple Clinical Programs, it is possible that more than one program may attempt to reserve a CB unit for that patient. Such simultaneous reservation must be prevented to avoid logistical problems with providing the correct program with information regarding the unit and providing the unit itself.

The CBB should validate the process for listing, search, selection, reservation, release, and distribution to document that the process properly identifies the CB unit and protects unit integrity.

The electronic record system's algorithm must be validated to list CB units properly when performing recipient searches against the registered inventory.

Evidence:

The CBB should show the inspector written agreements between the CBB and registry that describe the registry's responsibilities.

E2: REVIEW OF CORD BLOOD UNIT RECORDS

STANDARD:

E2.1 The CBB shall have policies and Standard Operating Procedures for the comprehensive review of CB unit records, including at a minimum:

Explanation:

The CBB shall assess the safety of CB units prior to making them available for human use. Even if a family is considering the use of a related unit, the transplant physician may want to compare it to unrelated units prior to treatment in case a better choice is available. A better comparison (and, consequently, better results) is only possible if all the available information is the same.

Example(s):

The information that must be reviewed prior to registering a CB unit is listed in the following Standards. The details for each are provided in Part D.

STANDARD:

E2.1.1 Results of tests outlined in the Testing Requirements table in Appendix IV.

E2.1.2 Infant donor's ethnicity/race.

E2.1.3 Infant donor's gender.

E2.1.4 Infant donor's physical examination.

E2.1.5 Maternal risk factors for transmission of communicable disease.

E2.1.6 Family medical history for transmissible genetic and malignant diseases.

E2.1.7 Hemoglobinopathy, if known.

E2.1.8 Consents.

E2.1.9 Processing and cryopreservation parameters.

E2.2 Unrelated CB units shall be made available for search on a registry or the CBB's inventory only after processing, medical, and quality review has been completed.

Explanation:

The review of processing records, overall medical review, and quality review must be completed prior to the release of the CB unit. If there are discrepancies between the medical and quality reviews, they must be resolved prior to listing the unit.

STANDARD:

E2.3 *The nature of ineligible or nonconforming CB units shall be disclosed to the registry and/or the requesting party.*

Explanation:

Prior to listing a CB unit for search, CBB must review the unit record for nonconformances. For unrelated CB units, nonconformities must be provided to the registry to facilitate efficient search and selection processes for interested Clinical Programs. There are also situations when information about a unit is requested from an entity or individual other than a registry, such as physicians considering related administration or seeking a unit with a rare HLA type. Nonconformances must also be provided to those parties.

Example(s):

Examples of nonconforming CB units include:

- Units without an attached segment,
- Units with an incomplete maternal health questionnaire,
- Units with incomplete infectious disease testing,
- Units with positive infectious disease markers.

E3: CORD BLOOD UNIT SELECTION AND RELEASE FOR ADMINISTRATION

STANDARD:

E3.1 *The CBB shall indefinitely retain documentation of requests for CB units, requests for samples, requests for and results of testing, and records of transportation and shipping of CB units and samples between facilities.*

Explanation:

A CBB needs to be able to confirm that the information provided to the Clinical Program or to the registry(ies) is correct and complete. Components of this system need to account for duplicate searches by several Clinical Programs or registries, prevention of reserved CB units from further requests, and removing units from reserved status. If units are in multiple registries and in an internal release program, there must be a mechanism for the CBB to inform all involved registries of a change in unit availability.

STANDARD:

E3.2 *Before a CB unit is released, a sample obtained from a contiguous segment of that CB unit shall be tested to verify HLA typing and, if possible, cell viability.*

E3.2.1 *The CB unit shall be tested to verify HLA typing at least once after a CB unit is cryopreserved.*

E3.2.2 *If a contiguous segment was never available, another validated method shall be used to identify the CB unit.*

E3.2.3 *Any histocompatibility discrepancy shall be resolved and communicated to the registry and the Clinical Program.*

E3.2.4 *Where proof of identity has been obtained for the CB unit, a copy of the report shall be provided to the Clinical Program upon request for the CB unit.*

Explanation:

Repeat HLA typing, including typing of a sample from a contiguous segment, is a check of CB unit identity and also a verification of the HLA type.

CB units are manufactured with a limited number of attached segments when cryopreserved. Verification HLA typing must be performed on an attached segment to verify the initial HLA typing obtained on the unit and listed on the registry. Verification typing is typically performed when a unit is under consideration for a recipient for administration. Most Clinical Programs obtain verification typing on several units before they select the optimal unit for their patient. Thus, a given unit may be typed but not selected for administration by the initial Clinical Program requesting the first verification typing. Due to the limited number of segments attached to a given unit, verification HLA typing may not be repeatable by subsequent Clinical Programs interested in the unit once the initial verification is performed. A unit that has been previously typed for verification may be selected by a subsequent Clinical Program without repeating this test, as long as the verification typing results match the original typing on the unit and are provided to the subsequent Clinical Program.

If a contiguous segment is not available for older units banked prior to FACT-NetCord accreditation, there must be an approach defined by the CBB to confirm CB unit identity prior to release. In addition, the Clinical Program must be notified well in advance so plans can be made to accept or decline the unit.

Example(s):

If the volume of a segment allows only a small amount of DNA to be extracted, it may be acceptable to perform a broad range of HLA typing on a non-contiguous reference sample and then verify this typing by a more limited panel of HLA tests performed on the contiguous segment. Other additional genetic markers, such as short tandem repeats (STRs), can also be used to confirm identity.

STANDARD:

E3.3 *At the time of selection for administration, the CBB and/or registry shall provide all technical data to the Clinical Program, including at a minimum:*

Explanation:

The information that must be provided is listed below. All of this information may not be included on the registry, but the CBB must keep the information in a way that allows it to provide it to the Clinical Program upon selection. The CBB may also delegate this task to a registry, if used.

STANDARD:

E3.3.1 *Results of tests outlined in the Testing Requirements table in Appendix IV.*

E3.3.1.1 *There shall be documentation of notification of the physician using the CB unit of the results of all testing and screening as required by Applicable Law.*

E3.3.1.2 *In the case of incomplete donor eligibility, there shall be documentation that the donor eligibility was completed during or after use of the CB unit and that the physician using the CB unit was informed of the results of that determination as required by Applicable Law.*

Explanation:

When the transplant center selects a CB unit prior to high resolution testing, the CBB is expected to perform the testing at some point, acknowledging that the result may not be available at the time that the unit is released.

Example(s):

CB units manufactured in or imported to the U.S. must follow the FDA donor eligibility requirements.

Refer to FDA's Guidance for Industry, Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) at

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM091345.pdf>.

STANDARD:

E3.3.2 *For related CB units with positive microbial tests documented in the CB unit record, antimicrobial sensitivities.*

Explanation:

It is understood that related CB units may be stored despite having positive microbial cultures. It is important that the Clinical Program and the patient be aware of culture results.

Specific unrelated donor eligibility requirements do not apply to related donors. However, if product testing (including microbial testing of the product) is performed, positive test results received on the CB unit should be reported in the summary of records.

Example(s):

A fact sheet describing the risks of using microbial positive CB for therapeutic use might be included with the release of the unit.

STANDARD:

E3.3.3 *Gender of the infant donor.*

E3.3.4 *Risks of communicable and/or genetic diseases disclosed by the maternal medical and genetic screening or clinical chart review and the results of any investigation or further testing performed.*

E3.3.4.1 *The CBB shall disclose to the Clinical Program if the genetic or medical history of a first-degree relative is unknown.*

Explanation:

If a Clinical Program requests a CB unit for which determination of risks of communicable disease transmission is not yet complete, the CBB must obtain approval for use of the unit from the recipient's physician, the CBB Medical Director or other designated physician, and the Quality Unit.

The CBB must make an attempt to elicit the medical and genetic history from all first-degree genetic relatives, including egg, sperm, or embryo donors. In some cases, the mother may not know the history of all relatives. This must be noted for further review by the CBB Medical Director, who will determine if the CB unit may or may not be stored.

Example(s):

In the U.S., CBBs must comply with 21 CFR 1271.60 when a CB unit with incomplete donor eligibility is released for administration.

STANDARD:

E3.3.4.2 *For related CB units, history of malignant or genetic disease in a first degree relative of the infant donor shall be disclosed to the Clinical Program.*

Explanation:

Even if the risk has been excluded, the CBB must still disclose history of malignant disease in a first degree relative to the Clinical Program.

STANDARD:

E3.3.5 *The method of CB unit processing.*

E3.3.6 *Any variances in collection, processing, testing, cryopreservation, storage, transport, or shipping procedures that may influence the integrity or quality of the CB unit.*

Explanation:

This should include the basic processing information, such as depletion of red cells, plasma, or both; the name and volume of solutions added to the CB unit during processing, and the freezing technique. Any risk or variance as determined by the CBB that may influence the selection decision by the Clinical Program must be communicated early in the search process so that the patient treatment plans are not adversely impacted.

STANDARD:

E3.3.7 *Physical characteristics of the CB unit, including at a minimum the number and type of bags or compartments used for storage.*

E3.3.8 *Information about the type of cassette in which the CB unit will be shipped.*

E3.3.9 *Instructions for storage of the CB unit.*

Explanation:

The intent of this standard is to communicate storage expectations to the receiving facility so they can be prepared to hold the CB unit in the appropriate manner prior to administration. Providing the physical dimensions of the bag and canister may be helpful to the receiving facility in determining the storage location of the unit.

STANDARD:

E3.3.10 *Instructions for thawing and administering the CB unit, including expected range of results based upon CBB internal validation results or published documentation.*

Example(s):

CBBs with a BLA in the U.S. are required to validate the thaw and wash of the final CB unit.

E4: CORD BLOOD UNIT DISTRIBUTION TO A CLINICAL PROGRAM

STANDARD:

E4.1 *The CBB shall obtain, in written or electronic form, a request from the transplant physician, designee, or registry for distribution of the CB unit prior to release of the CB unit.*

E4.2 *The CBB Medical Director or designee and the Quality Unit shall conduct a comprehensive record review, in accordance with Applicable Law, prior to distribution of a CB unit to a Clinical Program and document this review.*

Explanation:

Distribution includes the transportation or shipping of a CB unit. The review required in this section is often referred to as a CBB's process for ensuring that all elements of collection, processing, testing and storage have been evaluated and determined to meet established safety, potency, identity, and quality criteria.

Evidence:

The CBB should discuss with inspectors the laws and regulations applicable to its activities.

Example(s):

The evaluation includes determination of donor eligibility as defined by the FDA for non-U.S. CBBs exporting CB units to the U.S. Refer to FDA's Guidance for Industry, Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/PS) at <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM091345.pdf>.

STANDARD:

E4.3 When the maternal medical or genetic screening history indicates potentially transmissible disease or when there is a positive or indeterminate communicable disease test result:

E4.3.1 A CB unit intended for allogeneic use with incomplete donor eligibility or determined to be ineligible shall be distributed only if there is documented urgent medical need for the CB unit. Documentation shall include, at a minimum, the approval of the recipient's physician, the CBB Medical Director, and the Quality Unit.

E4.3.2 If donor eligibility is incomplete, and completion of screening and testing is possible, the eligibility determination shall be completed and the results provided to the recipient's physician.

Explanation:

This standard pertains to situations where use of an ineligible CB unit is permissible with urgent medical need based on the unavailability of another suitable donor.

STANDARD:

E4.4 At the time of distribution to a Clinical Program, the CB unit bag shall be labeled as required in the Cord Blood Unit Labeling table in Appendix II.

Explanation:

Information that is required to be attached to the CB unit must be attached securely with a tie tag. Accompanying information must be enclosed in a sealed package to accompany the unit.

Attached segments must be appropriately identified to allow accurate tracing to the CB unit in the event the segment becomes detached from the unit (for example, if they become detached during the cryopreservation procedure). The segment should be identified in a manner that allows traceability of all steps performed on the CB unit and donor.

Example(s):

One way to comply with this standard is through the use of labels or stickers; however, the CBB may decide how to identify the sample as long as it accurately traces it to the CB unit.

STANDARD:

E4.5 A circular of information or package insert and instructions for handling, thawing, and using the CB unit, including short-term storage and preparation for administration, shall accompany the CB unit.

Explanation:

The intent of this standard is to require that the CBB gives the Clinical Program information on how to handle and use the CB unit.

Example(s):

A “Circular of Information for the Use of Cellular Therapy Products” document (prepared jointly by the AABB, American Association of Tissue Banks, American Red Cross, American Society for Blood and Marrow Transplantation, American Society for Apheresis, America’s Blood Centers, Foundation for the Accreditation of Cellular Therapy, ICCBBA, International Society for Cellular Therapy, and National Marrow Donor Program) contains information (including indications, contraindications, and cautions) that is suitable for this purpose. This document can be found on the FACT website at www.factwebsite.org > Education and Resources > Resources.

For U.S. CBBs that wish to submit a BLA, the FDA guidance, “*Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications*,” suggests validating a thawing process that results in the recovery of at least 70 percent of the viable nucleated cells that were present before cryopreservation. Instructions for the validating thawing process must be provided to the Clinical Program if the thawing will take place at that facility.

Because there have been documented adverse events related to the administration of CB units containing red blood cells, the *FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration* requires washing of cellular therapy products that have not been red cell reduced, and this practice is also recommended for products that have been red cell reduced. In the case of double CB transplants, the Clinical Program must wait to administer the second unit until it is determined that the first unit was administered safely with no adverse events. It is recommended that CBBs include these same instructions to Clinical Programs when distributing a CB unit for administration.

STANDARD:

E4.6 Elements detailed in the Accompanying Documents at Distribution table in Appendix III shall accompany the CB unit at distribution to a Clinical Program according to Applicable Law.

Explanation:

The records referred to in this standard are source documents and the information used to perform the donor eligibility determination.

These Standards allow for CB units obtained from ineligible donors to be distributed for infusion provided that there is documented medical need that the unit be used despite the potential risks to the recipient. Use of CB units from an ineligible donor requires documented approval of the CBB Medical Director that includes the reason that the donor was ineligible, and documentation that the physician administering the CB unit has been notified of all testing and screening results.

CB units that are needed for infusion before all required donor screening and testing are complete may also be distributed provided that the distribution documents (for example, the product infusion form) include a statement that eligibility determination is not complete and a list of required testing or screening that has not been completed. The physician using the unit must be notified of all results of screening and testing that has been completed, and also be notified of the incomplete testing or screening. It should be the CBB Medical Director in concert with the attending physician, rather than the CB Processing Facility personnel, who determine if a request for unit release prior to completion of

testing is warranted. Such a situation would likely fall under the category of a non conforming unit and would require exceptional release and CBB Medical Director agreement.

The CB Processing Facility must inform the transplant physician of the results of any testing or screening that was completed after the CB unit was distributed. The provision of this information must be documented in the processing records. If any result is positive, it is the responsibility of the physician to notify the recipient and to document patient notification in the clinical record.

STANDARD:

E4.7 A practice CB unit should be available if requested by the Clinical Program.

E4.7.1 The practice CB unit shall be clearly labeled with the statement, "For Nonclinical Use Only."

Explanation:

A CBB may offer CB units otherwise unsuitable for transplant to Clinical Programs not familiar with a thawing method or a particular CBB's units to practice thawing. Requests for these units may also be submitted for training, competency, or validation purposes. The unit offered for these purposes must be clearly labeled "For Nonclinical Use Only."

STANDARD:

E4.8 The CB unit should be received by the Clinical Program prior to initiation of the recipient's preparative regimen unless approved by the transplant physician.

E5: TRANSPORTATION AND SHIPPING OF CRYOPRESERVED CORD BLOOD UNITS

STANDARD:

E5.1 Procedures for transportation and shipping of cryopreserved CB units shall be validated.

E5.2 The transit time between the CBB and other facilities shall be minimized.

E5.2.1 There shall be written plans for alternative transportation or shipping in an emergency.

Explanation:

Same day transport and shipping arrangements are encouraged. CBBs should educate their couriers on how to handle the CB unit and the importance of preventing tipping.

Registries may perform distribution for CBBs and they are required to comply with this requirement.

Example(s):

An example of a plan for alternative transportation or shipping in an emergency is utilizing a different courier or flight.

STANDARD:

- E5.3 *Cryopreserved CB units shall be transported or shipped in a liquid nitrogen-cooled dry shipper that contains adequate absorbed liquid nitrogen and has been validated to maintain a temperature of -150°C or colder for at least 48 hours beyond the expected time of arrival at the receiving facility.*
- E5.3.1 *The dry shipper shall contain an electronic data logger that continuously monitors temperature throughout the transportation or shipping period.*
- E5.3.2 *The transport or shipping methods shall conform to Applicable Law regarding the mode of transportation or shipping of such devices.*
- E5.3.3 *The dry shipper shall be labeled in accordance with Applicable Law regarding the cryogenic material used and the transportation or shipping of biologic materials.*
- E5.3.4 *All container lids shall be secured.*
- E5.3.5 *The outer container shall be labeled with the information required in the Cord Blood Unit Labeling table in Appendix II.*
-

E6: TRANSPORTATION AND SHIPPING RECORDS REQUIREMENTS

STANDARD:

- E6.1 *Transportation and shipping records shall permit the tracking and tracing of the CB unit from the CBB to its final destination.*
- E6.2 *The package shall include a list identifying the CB unit, intended recipient, intended destination, transportation and shipping records, and any warnings and other associated documents.*
- E6.3 *Transportation and shipping records shall document:*
- E6.3.1 *The CBB responsible for transporting or shipping the CB unit.*
- E6.3.2 *The date and time of packaging of the CB unit at the CBB.*
- E6.3.3 *The date and time the package left the CBB.*
- E6.3.4 *The identity of the courier and tracking information.*
- E6.3.5 *The date and time of receipt of the package.*
- E6.3.6 *Maintenance of the temperature within the specified range throughout the period of transportation or shipment.*

Explanation:

Documenting the time the CB unit is packaged is necessary to verify that transportation or shipping occurred during the appropriate timeframe. Outer containers are only validated for a certain amount of time; if the unit is within a container for a duration longer than what has been validated, it may be compromised. Records of dates and times also document the chain of custody of the unit.

CB units are often distributed to other countries, and distributing CBBs must be aware of the export and import requirements of both countries as applicable. Countries often have specific requirements for documentation; these can be found on the countries' applicable websites.

Example(s):

The CBB should analyze trends for the CB units shipped and verify consistency with the validated time frame to sustain desired temperature. Tracking information including temperature, integrity of the container, and CB unit inspection at receipt during transportation can be in multiple forms, including online or in paper format.

STANDARD:

E6.4 The CBB shall have policies and Standard Operating Procedures to obtain the following data from the receiving facility about the CB unit upon receipt:

E6.4.1 Date and time of receipt.

E6.4.2 Identity of the personnel receiving the CB unit.

E6.4.3 Integrity of the dry shipper.

E6.4.4 Verification of appropriate temperature range.

E6.4.5 Integrity of the CB unit.

E6.4.6 Verification that required documentation is available.

E6.5 If an unrelated CB unit has left the CBB premises, the CB unit shall not be returned to the general CBB inventory.

Explanation:

Return of unrelated CB units is not permitted by these Standards in part as a protection for the CBB. Clinical Programs needs to be certain that they are prepared to accept responsibility for the package prior to its release from the CBB.

Receiving the data about the CB unit upon receipt from either registries or the Clinical Program is acceptable. The CBB must have a process in place to attempt to obtain the information from the program.

Example(s):

In the event that a patient dies or is considered no longer eligible for transplant, it is the Clinical Program's responsibility to determine how to handle the CB unit.

E7: CLINICAL OUTCOME DATA

STANDARD:

E7.1 The CBB shall have a policy or Standard Operating Procedure to request the following information within the recommended time period for every CB unit released for administration for hematopoietic reconstitution :

E7.1.1 Viable nucleated cell yield results on the thawed CB unit.

E7.1.2 Complaints associated with the CB unit.

E7.1.3 Adverse events associated with administration of the CB unit.

E7.1.4 Time to neutrophil and platelet engraftment.

E7.1.4.1 For allogeneic CB units, data should include engraftment and chimerism.

E7.1.4.2 In the case of more than one graft product used for administration, the CBB should collect and document that information and, if possible, which product engrafted.

E7.1.5 Survival rates annually at a minimum.

E7.1.6 GVHD results annually at a minimum.

E7.1.7 Microbial screening.

E7.1.8 Administered cell dose.

Explanation:

There are a variety of ways that chimerism and GVHD are reported by Clinical Programs. CBBs should keep track of as much information as they can regarding how the results were found. For example, if the Clinical Program provides the CBB with information on how it scored GVHD, the CBB should maintain that information.

Example(s):

CBBs may define engraftment as the time period for the hematopoietic recovery at the time point of the first 3 consecutive days with a count $\geq 0.5 \times 10^9/L$ for neutrophils and of the first 7 consecutive days with $\geq 20 \times 10^9/L$ for platelets without transfusional support.

STANDARD:

E7.2 *The CBB shall have a policy to request outcome data that is relevant to other uses for which a CB unit was released.*

KEY PERSONNEL REQUIREMENTS

	Education and Experience	Job Responsibilities	Continuing Education (A minimum of 10 hours annually in the any combination of these disciplines)
CBB Director	<ul style="list-style-type: none"> • Doctoral degree in medicine or in a related scientific field • Training and a minimum of two (2) years of experience in immunogenetics of transplantation¹, basic or clinical immunology, immunohematology, basic or clinical hematology, transfusion medicine, blood or tissue banking, or cryobiology 	<ul style="list-style-type: none"> • Final responsibility for CBB operations • Overall CBB compliance with these Standards, including all components of the CBB's policies and Standard Operating Procedures 	CB banking; cellular therapy product collection, processing, and administration
CBB Medical Director	<ul style="list-style-type: none"> • Licensed physician • Training in hematopoietic cell transplantation or blood or tissue banking 	<ul style="list-style-type: none"> • Donor recruitment • Donor eligibility • Medical aspects of CB collection procedures, CB processing procedures, and review of the release and outcome data of the CB unit, including compliance with these Standards 	Donor safety; CB banking; cellular therapy product collection, processing, and administration
CB Collection Director	<ul style="list-style-type: none"> • Health care professional • Bachelor's degree • Training and experience in hematopoietic cell transplantation, blood and tissue banking, or CB collection 	<ul style="list-style-type: none"> • Collection activities • Communication with individual CB Collection Sites 	Donor safety; CB banking; cellular therapy product collection, processing, and administration
CB Processing Facility Director	<ul style="list-style-type: none"> • Relevant doctoral degree • Qualified by training or experience for the scope of activities carried out in the CB Processing Facility 	<ul style="list-style-type: none"> • All operational aspects of all procedures related to receipt, testing, processing, cryopreservation, storage, release, and distribution of CB units and administrative operations of the CB Processing Facility, including compliance with these Standards 	CB banking; cellular therapy product collection, processing, and administration
Quality Unit Manager²	<ul style="list-style-type: none"> • Relevant training in quality management 	<ul style="list-style-type: none"> • Establish and maintain systems to review, modify as necessary, approve, and implement all policies and Standard Operating Procedures • Monitor performance of the QM Program, the quality of the CB units, and compliance with these Standards 	Quality management; CB banking; cellular therapy product collection, processing, and administration

¹If the CBB Director does not have specific training and expertise in HLA, the CBB shall confirm HLA expertise is available and utilized by the CBB.

²The Quality Unit Manager shall be a different individual from the CBB Director, CBB Medical Director, CB Collection Director, and the CB Processing Facility Director.

Explanation:

The *CBB Director's* expertise must extend to the use of CB units for clinical transplantation or regenerative medicine. The director must have training and a minimum of two years of experience in the fields listed in this standard. Furthermore, the CBB Director has responsibility for the HLA typing, listing, search, selection, reservation, release, and distribution of the CB units and must have HLA typing expertise or confirm that such expertise is available to the CBB.

The *CBB Director* is responsible for the entire process of cord blood collection, banking, and release for administration and has a hierarchical lead over the CB Collection Director and CB Processing Facility Director for all activities related to cord blood donor management and collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, and distribution of CB units.

If the CBB has an IRB, the *CBB Director* is responsible for collaborating with the quality unit on submissions to the IRB as part of his/her responsibility for compliance with Applicable Law and clinical performance.

The *CBB Medical Director* is responsible for medical aspects of cord blood collection, banking, and release. Part of this responsibility is to review information from Clinical Programs regarding the medical aspects of the administration of the CB unit. As a physician, the CBB Medical Director has the expertise to review the data and determine if a unit is potentially responsible for any adverse events.

The *CB Collection Director* must maintain communication between the CBB and each CB Collection Site for which he/she is responsible. A different CB Collection Director for each site is not required; one person can direct multiple sites.

The *CB Collection Director* does not need to be licensed in the jurisdiction of the CB collection or be on the staff of the CB Collection Site; however, he/she must meet Applicable Law with respect to licensure. Some jurisdictions may consider the activities of this person to be the practice of medicine or another regulated profession, which could require licensure.

The *CB Processing Facility Director* should be experienced in blood, progenitor cell, or tissue processing for clinical use and needs to be qualified in aspects such as traceability, volume reduction, cellular qualification, virology testing, cryobiology, long-term storage facilities, and distribution for human administration.

Evidence:

The CBB will be asked to submit documentation of the degrees, evidence of training, years of experience, and publications. Given the growing uses of CB units, CBB Directors may come from a wide range of professional backgrounds. If the qualifications of a CBB Director are unclear, the Accreditation Committee will review the documentation and make a recommendation to the FACT and NetCord Boards of Directors.

Documentation that would provide evidence of responsibilities includes a job description, attendance at meetings, signatures on forms and reports, etc.

Example(s):

Typically, the HLA typing responsibilities are delegated to the HLA testing laboratory and the CBB Director is responsible for ensuring that the typing is done correctly, the results match the original typing results (for verification typing), and that the results meet release criteria. The CBB may also delegate the HLA typing responsibilities to experts from a national registry. Many different arrangements may satisfy this requirement as long as there is an individual with the appropriate training and expertise responsible for this aspect of CB banking.

This page intentionally left blank.

APPENDIX II

CORD BLOOD UNIT LABELING

Label Element	Partial label	At completion of collection	Outer container labeling at transport or shipping from collection	At completion of processing prior to cryopreservation	At distribution to Clinical Program	Outer container labeling at distribution to Clinical Program
Unique numeric or alphanumeric identifier	AT	AF		AF	AF	
Proper name of product ²	AT	AF		AF	AF	
Product attributes (manipulations) ²				AC	AC	
Statement Related Donor ¹	AT	AT		AF	AF	
Statement "Autologous Use Only" ¹					AT	
Statement "Caution: New Drug – Limited by Federal (or United States) law to investigational use." ⁵					AT	
Statement "Rx Only" ⁵ (Rx = Prescription)					AT	
Collection site identifier		AT				
Date of collection		AT		AC	AC	
Time of collection and time zone, if different from the CB Processing Facility		AC				
Name and volume or concentration of additives				AC	AC	
Name and volume or concentration of anticoagulants		AF		AC	AC	
Recommended storage temperature		AT		AF	AF	
Donor name (Related CB units) ¹		AT		AT	AT	
Recipient family or individual name and unique identifier, if known ¹		AT		AT	AT	
Recipient's name and unique identifier					AT	
Volume or weight of the CB unit at the end of collection				AC	AC	
Volume or weight of the CB unit at the end of processing				AC	AC	
Date of cryopreservation				AC	AC	
ABO group and Rh type					AC	
HLA phenotype					AC	
Number of nucleated cells post processing				AC	AC	
Gender of CB unit infant donor				AC	AC	
Identity of the CBB ³				AF	AF	
Statement "Properly Identify Intended Recipient and Product"					AC	
Statement "For Use By Intended Recipient Only" (Allogeneic CB units) ¹					AC	
A statement indicating that leukoreduction filters should not be used					AC	
Statement "Do Not Irradiate"					AC	
Statement "For Nonclinical Use Only" ¹					AC	
Biohazard legend and/or warning labels (see B6.6.3) ¹		AC		AC	AC	
Donor eligibility summary. See Appendix III.					AC	
Date and time of distribution					AC	AF
Shipping facility name, address, phone number			AF			AF
Receiving facility name, address, phone number			AF			AF
Identity of person or position responsible for receipt of the shipment			AF			AF
Statement "Do Not X-Ray" ⁴			AF			AF
Statements "Medical Specimen", "Handle With Care" ⁴			AF			AF
Statement indicating Cord Blood for Transplantation						AF
Shipper handling instructions ⁴			AF			AF

¹If applicable.

²Product proper names, attributes, and manipulations are listed in Chapter Three of the *ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions*. Available: <http://www.iccbba.org/standardterminology.pdf>

³If there are CBBs of the same name in multiple countries, the identifier must distinguish between the CBBs on the label.

⁴If CB unit is shipped.

⁵If required by Applicable Law. ("Rx Only" means "Prescription Only".)

AF=Affix, AT=Attach or Affix, AC=Accompany or Attach or Affix; a CBB may choose to be more inclusive.

Facilities who have fully implemented ISBT 128 labeling shall follow the ISBT 128 Standard for the location of information.

Additional requirements may apply in accordance with Applicable Law.

APPENDIX III

ACCOMPANYING DOCUMENTS AT DISTRIBUTION

CB units collected in or designated for use in the U.S. shall be accompanied upon leaving the CBB with at least the elements detailed in the following table at a minimum as required by Applicable Law¹:

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

¹For autologous CB units, instructions for unit use to prevent the introduction, transmission, or spread of communicable diseases and for reporting serious adverse reactions or events to the distributing facility are always required for autologous products. Furthermore, a donor eligibility determination is not required by FDA. However, if any donor screening or testing is performed and risk factors or reactive test results are identified, accompanying documentation shall be provided.

²May only be distributed after release by the CBB Medical Director due to urgent medical need. For ineligible CB units or incomplete donor eligibility determination, the CB unit shall be shipped in quarantine. For units distributed prior to completion of donor eligibility, determination shall be completed if possible and the physician shall be informed of the results.

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

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

This page intentionally left blank.

APPENDIX IV

TESTING REQUIREMENTS

Test	CB Samples						Maternal Samples
	Pre-processing	Post-processing prior to cryopreservation	Any time prior to cryopreservation	On an appropriate sample type at any time prior to listing	Thawed segment or thawed representative sample prior to release to the Clinical Program	On an appropriate sample type at any time prior to release	Obtained within seven (7) days before or after CB collection
Cell Count							
CBC with differential	X						
Total nucleated cell count		X			Should be performed		
Nucleated red blood cell count		X					
Total CD34		X					
Total Viable CD34		X			Should be performed		
Viability							
% Viability of Total nucleated cell or % Viability of CD45		X					
% Viability of CD45					X		
% Viability of CD34		X			X		
CFU or other validated potency assay		Should be performed ¹			X		
HLA Tissue Typing							
Low Resolution: HLA-A, HLA-B, HLA-DRB1				X			
Low Resolution HLA-C				Should be performed			
High Resolution: HLA-A, HLA-B, HLA-DRB1						X	
High Resolution HLA-C						◆	
Verification Typing					X ²		
Infectious Disease³							
HIV 1				X ⁴			X
HIV 2				X ⁴			X
Hepatitis B				X ⁴			X
Hepatitis C				X ⁴			X
HTLV I				X ^{4,5}			X ⁵
HTLV II				X ^{4,5}			X ⁵
Syphilis				X ⁴			X
CMV				X ⁴			X
Additional tests ³				X ⁴			X
Other							
Microbial culture		X					
ABO/Rh blood group			X				
Hemoglobinopathy						◆	

X – All CB units regardless of intended use.

◆ - CB units for unrelated use only.

¹If post-processing testing was not performed historically, a potency assay must be performed prior to release for administration by the CBB.

²Verification of the HLA typing results can be performed at any resolution. A CBB may choose to perform this verification using the results of the high resolution HLA typing if that typing is performed on contiguous segments at the time of release to the Clinical Program. Verification typing shall be performed on a thawed segment or thawed representative sample.

³Appendix IV defines the minimum testing criteria for both cord blood and maternal blood samples. It is not possible to capture all regional variations in testing requirements. As such, additional tests for infectious transmissible agents may be required to be performed in accordance with Applicable Law or institutional policy. In certain circumstances, additional testing may be required depending on the donor's history and the characteristics of the tissue or cells donated (e.g. West Nile Virus, toxoplasma, CMV, EBV, *Trypanosoma cruzi* [*Chagas disease*]) and may include emergent disease testing.

⁴Each CB unit should be tested for evidence of infection for communicable disease agents using licensed donor screening tests when available according to Applicable Law. Per the EU Directive, required maternal testing is repeated on the CB unit if stored for a long period of time, or alternatively NAT technology is used to test the original maternal sample. Testing specifications vary from country to country. This testing must be performed prior to release for administration when testing is required by Applicable Law or institutional policy.

⁵In Europe, HTLV I is performed only on a selected donor population with increased risk of infection and HTLV II is not required per EU Directive.

In the U.S., the CBB may need to conduct more than one test to adequately and appropriately test for a single communicable disease agent or disease. Refer to the CBER website (fda.gov/BiologicsBloodVaccines) for a list of approved tests. Testing is performed following manufacturers' instructions using FDA-licensed, approved, or cleared donor screening tests for relevant communicable disease agents and diseases (RCDADs) as defined by U.S. FDA. FDA-licensed, approved, or cleared donor screening tests are available for WNV and HBV NAT and T. Cruzi testing may be implemented per facility-specific guidance prior to an FDA testing requirement.

In Europe, member countries of the European Union may introduce additional requirements. In some settings, testing by more than one method may be required for some infectious agents. This table is not intended to reflect all national variations but rather present general requirements within the EU. The tests must be carried out by a qualified laboratory, authorized as a testing center by the competent authority in the Member State, using CE-marked testing kits where appropriate. The type of test used must be validated for the purpose in accordance with current scientific knowledge.

APPENDIX V

SPECIFICATION REQUIREMENTS FOR CORD BLOOD UNITS STORED FOR CLINICAL ADMINISTRATION

Test	Unrelated Specification		Related Specification	
	Fresh Post-Processing Sample	Post-Thaw Attached Segment or Representative Sample Prior to Release	Fresh Post-Processing Sample	Post-Thaw Attached Segment or Representative Sample Prior to Release
Total nucleated cell count	≥ 5.0 x 10 ⁸		Enumerated	
Total nucleated cell recovery	Should be ≥60%		Should be ≥60%	
Total viability	≥ 85%		≥ 70%	
Viable CD34 count	≥ 1.25 x 10 ⁶			
Viability of CD34 cells	≥ 85%	≥ 70%	≥ 85%	≥ 70%
Viability of CD45 cells		≥ 40%		≥ 40%
CFU (or other validated potency assay) ¹		Growth (or positive result for potency)		Growth (or positive result for potency)
Microbial Screen	Negative for aerobes, anaerobes, fungus		Negative for aerobic and anaerobic bacteria and fungi – OR – identify and provide results of antibiotic sensitivities	
Donor screening and testing	Acceptable as defined by Applicable Law and NetCord-FACT Standards		Acceptable as defined by Applicable Law and NetCord-FACT Standards	
Identity		Verified		Verified

¹There should be evidence of potency by CFU or other validated potency assay on a fresh post-processing sample.

This page intentionally left blank.

ACKNOWLEDGEMENTS

Cord Blood Bank Standards Committee Leadership

Joseph Schwartz – Chair
Phyllis I. Warkentin - Co-Chair
Elizabeth J. Shpall - Co- Chair
Carolyn Keever-Taylor - Past Chair

QM and Operational Standards Subcommittee

Ngaire Elwood – Co-Chair
Jacqueline van Beckhoven – Co-Chair

Michele Carbone
Merry Duffy
Diane Fournier
Eliane Gluckman
Andreas Papasavvas
Sergio Luis Querol Giner
Robyn Lynette Rodwell
Elisabeth Semple
Arun Prasath Shanmugam
Bart Vandekerckhove
Roberto Waddington

Collection Subcommittee

Sue Armitage – Co-Chair
Rodica Ciubotariu – Co-Chair

Robin Berger
Heidi Elmoazzen
Kate Girard
Linda Kelley
Rachel Pawson
Tara Sadeghi
Del Steckler
Sergio Torloni

Processing Subcommittee

Gesine Koegler – Co-Chair
Joanne Kurtzberg – Co-Chair

Ed Brindle
Maria Vittoria Gazzola
Susana Gomez
Phillip Johnson
Elias Kalouche
Ann Kemp
Lucilla Lecchi
Nadim Mahmud
Dondi Pulse-Earle
Arun Prasath Shanmugam
Kristen Swingle
Marta Torrabadella-Reynoso

Staff

Andra Moehring
Kara Wacker

This page intentionally left blank.

Index

A

ABO group, 6, 170, 171, 200, 204
Accidents, 11, 31, 32, 33, 35, 43, 86
Accompany, 6, 7, 72, 73, 74, 85, 124, 126, 135, 143, 189, 190, 201, 202
Accreditation, 6, 15, 21, 22, 30, 60, 61, 65, 81, 82, 92, 96, 133, 185, 197, 216
Administration, 6, 7, 8, 9, 15, 16, 17, 22, 23, 25, 31, 32, 34, 35, 40, 41, 44, 47, 48, 49, 56, 57, 63, 102, 111, 113, 119, 139, 154, 159, 161, 163, 164, 166, 172, 173, 174, 177, 178, 180, 181, 182, 184, 185, 187, 188, 189, 190, 194, 196, 197, 205, 206
Adverse event, 7, 16, 31, 32, 33, 34, 35, 39, 42, 43, 62, 76, 77, 85, 89, 104, 114, 115, 126, 151, 190, 194, 197
Adverse reaction, 7, 32, 33, 34, 35, 86, 202
Affix, 6, 7, 8, 13, 68, 69, 72, 73, 124, 126, 201
Agreement, 9, 10, 15, 21, 22, 25, 30, 40, 41, 43, 51, 56, 58, 81, 82, 86, 93, 94, 96, 97, 98, 99, 101, 108, 109, 110, 111, 113, 141, 142, 143, 167, 169, 182, 191
Alarm, 132, 137, 159, 161, 162, 163
American Society for Histocompatibility and Immunogenetics (ASHI), 6, 60
Aseptic technique, 7, 123, 145
Attach, 6, 7, 8, 9, 12, 17, 48, 69, 70, 72, 73, 74, 83, 124, 126, 143, 149, 150, 165, 184, 185, 189, 201, 206
Audit, 8, 14, 23, 30, 31, 33, 38, 39, 42, 43, 51, 62, 75, 78, 80, 86, 89, 90, 91
Available for distribution, 8, 86, 159

B

Biohazard, 8, 43, 45, 49, 50, 72, 73, 108, 137, 139, 141, 200
Biological product deviation, 8, 31, 32, 33, 35, 43
Bone marrow. *See Marrow*

C

Calibration, 8, 37, 76, 77, 87, 93, 169
CB unit, 6, 8, 9, 10, 13, 14, 15, 16, 20, 21, 23, 24, 25, 26, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 44, 45, 46, 47, 48, 49, 50, 56, 57, 58, 59, 60, 61, 62, 63, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 78, 79, 80, 81, 82, 83, 85, 86, 87, 88, 89, 92, 93, 94, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 111, 112, 113, 114, 115, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 181, 182, 183, 184, 185, 186, 187, 188,

189, 190, 191, 192, 193, 194, 195, 196, 197, 200, 201, 202, 205
allogeneic, 7, 11, 17, 20, 21, 44, 48, 58, 59, 60, 63, 71, 72, 73, 74, 99, 119, 164, 165, 167, 168, 181, 189, 190, 194, 200, 202
autologous, 8, 11, 17, 20, 33, 48, 58, 72, 73, 181, 200, 202
related, 6, 7, 8, 9, 11, 13, 15, 20, 21, 24, 25, 32, 33, 37, 42, 47, 54, 57, 58, 60, 62, 63, 64, 65, 66, 68, 74, 80, 81, 84, 85, 86, 87, 92, 93, 94, 96, 97, 98, 103, 111, 112, 113, 114, 118, 126, 128, 140, 142, 143, 146, 147, 148, 156, 160, 164, 166, 167, 168, 169, 171, 173, 174, 176, 182, 183, 184, 186, 187, 190, 196, 197, 200, 206
unrelated, 7, 8, 11, 20, 21, 35, 48, 57, 58, 59, 62, 63, 65, 71, 74, 80, 81, 86, 92, 96, 97, 98, 99, 111, 113, 114, 119, 121, 133, 142, 143, 146, 147, 148, 152, 156, 159, 164, 165, 167, 168, 170, 172, 173, 174, 177, 181, 182, 183, 184, 186, 190, 193, 205, 206
CB unit search, 7, 9, 12, 15, 16, 20, 21, 30, 32, 44, 47, 48, 57, 83, 87, 106, 174, 180, 181, 182, 183, 184, 187, 197
CD34, 8, 80, 88, 128, 144, 145, 146, 147, 149, 165, 166, 204, 206
CD45, 145, 146, 204, 206
Chagas disease. *See Trypanosoma cruzi*
Chimerism, 194
Cleaning, 45, 49, 77, 84, 87, 99, 104, 106, 108, 135, 141, 145
Clinical Program, 8, 20, 34, 40, 41, 48, 49, 54, 57, 61, 73, 75, 81, 82, 85, 93, 117, 150, 154, 170, 171, 172, 173, 174, 178, 180, 181, 182, 184, 185, 186, 187, 188, 189, 190, 191, 193, 194, 197, 200, 204, 205
Collection kit, 8, 55, 57, 97, 101, 102, 103, 105, 127, 142
Collection procedure, 10, 57, 86, 100, 103, 122, 196
Collection Site, 7, 9, 10, 21, 22, 24, 28, 42, 43, 44, 46, 47, 51, 53, 55, 56, 57, 58, 61, 71, 72, 73, 79, 86, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 110, 111, 123, 124, 125, 126, 127, 129, 196, 197
fixed collection, 24, 55, 56, 57, 58, 92, 96, 98, 101, 105, 111, 127
non-fixed collection, 24, 55, 56, 57, 92, 96, 105
Colony forming units, 6, 8, 80, 128, 144, 145, 146, 170, 204, 206
Communicable disease, 8, 11, 12, 13, 15, 44, 47, 56, 58, 59, 72, 73, 75, 78, 83, 99, 105, 107, 112, 115, 117, 118, 119, 120, 121, 139, 140, 148, 156, 157, 158, 171, 175, 176, 177, 183, 187, 189, 202, 205
Competency, 9, 12, 14, 25, 26, 46, 56, 57, 84, 86, 90, 91, 92, 96, 97, 104, 105, 107, 133, 140, 141, 153, 158, 175, 176, 191, 205
Complaint, 9, 31, 32, 33, 35, 38, 41, 43, 194

Confidentiality, 29, 45, 61, 71, 85, 89, 111, 114
Consent. *See* Informed consent
Container, 7, 8, 13, 15, 68, 69, 73, 74, 100, 102, 126, 127,
128, 129, 130, 139, 142, 146, 149, 192, 193, 200
Contamination. *See* Sterility
Corrective action, 10, 31, 32, 33, 34, 38, 75, 76, 123, 126
Creutzfeldt-Jakob disease, 119
Cryopreservation, 7, 9, 10, 14, 17, 20, 21, 22, 30, 32, 44, 47,
57, 66, 69, 72, 73, 74, 78, 79, 80, 81, 83, 87, 132, 134,
140, 143, 144, 145, 146, 147, 148, 149, 152, 153, 154,
155, 156, 158, 159, 160, 161, 165, 166, 167, 169, 171,
173, 180, 181, 183, 184, 185, 187, 189, 190, 191, 192,
196, 197, 200
Cytomegalovirus, 165, 176, 177

D

Delivery, 7, 10, 13, 43, 46, 47, 48, 61, 70, 71, 102, 107, 111,
117, 118, 119, 120, 121, 122, 124, 135, 152, 158, 168,
170, 172, 176
ex utero, 9, 56, 115
in utero, 9, 20, 56, 121
Designee, 10, 23, 32, 33, 34, 39, 66, 67, 82, 92, 104, 139,
155, 156, 157, 167, 169, 177, 188
Deviation, 8, 10, 17, 33, 43, 147, 159
Director, 9, 22, 23, 24, 25, 27, 30, 32, 33, 34, 35, 38, 39, 42,
51, 58, 59, 66, 67, 82, 92, 104, 117, 133, 139, 143, 144,
155, 156, 157, 169, 173, 191, 196, 197
CB Processing Facility Director, 22, 25, 133, 139, 143,
169, 171, 196, 197
CBB Director, 22, 23, 24, 27, 32, 33, 34, 35, 38, 39, 42,
51, 66, 67, 82, 92, 139, 155, 156, 157, 196, 197, 198
CBB Medical Director, 22, 58, 59, 117, 157, 170, 173,
177, 187, 188, 189, 190, 196, 197, 202
Disposal, 20, 43, 45, 49, 50, 57, 66, 84, 108, 113, 137, 139,
141, 142, 156, 164, 166, 167, 168, 177
Disposition, 10, 13, 33, 40, 45, 49, 57, 69, 70, 78, 87, 107,
108, 132, 139, 140, 156, 157, 163, 167, 177
Distribution, 7, 8, 9, 10, 13, 14, 16, 20, 21, 25, 28, 30, 32, 42,
49, 55, 56, 57, 65, 69, 72, 73, 74, 85, 86, 87, 102, 105,
124, 125, 127, 133, 134, 142, 156, 159, 173, 180, 181,
182, 188, 189, 190, 191, 193, 196, 197, 200, 202
Donor, 7, 8, 9, 10, 11, 12, 13, 14, 16, 20, 21, 22, 23, 25, 26,
30, 31, 32, 34, 40, 43, 44, 46, 47, 48, 57, 58, 59, 60, 61,
64, 68, 70, 71, 72, 73, 74, 80, 82, 85, 87, 89, 93, 94, 95,
96, 97, 98, 99, 101, 102, 104, 105, 106, 107, 109, 110,
111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121,
122, 123, 124, 128, 142, 143, 145, 146, 147, 152, 157,
158, 164, 165, 166, 167, 168, 170, 171, 172, 174, 175,
176, 177, 178, 186, 187, 188, 189, 190, 196, 197, 200,
202, 205, 206
infant donor, 7, 9, 10, 11, 12, 13, 16, 40, 43, 44, 46, 47,
48, 58, 61, 70, 71, 85, 95, 98, 104, 105, 106, 107, 109,

111, 112, 113, 114, 115, 116, 118, 119, 120, 121, 124,
169, 174, 177, 181, 183, 186, 187, 200
maternal donor, 10, 11, 12, 16, 57, 58, 80, 102, 111, 112,
113, 115, 118, 121, 122, 124, 167, 169, 171, 175, 176
Donor eligibility, 7, 12, 43, 46, 58, 59, 71, 80, 82, 85, 105,
106, 113, 114, 116, 118, 119, 121, 171, 176, 186, 187,
188, 189, 190, 196, 200, 202
Donor evaluation, 58, 95, 114, 115, 175

E

Eligibility. *See* Donor eligibility
Engraftment, 11, 17, 41, 144, 170, 172, 194
Equipment, 8, 14, 15, 19, 29, 34, 35, 37, 38, 39, 45, 49, 50,
52, 56, 61, 65, 74, 75, 76, 77, 84, 85, 87, 93, 99, 100, 101,
108, 123, 134, 135, 136, 137, 138, 141, 145, 148, 156,
169
Error, 11, 31, 32, 33, 35, 43, 67, 68, 70, 71, 75, 86, 89, 145,
181
Ethics Committee, 12, 35, 62, 147
European Federation for Immunogenetics (EFI), 6, 60
Expiration, 78, 79, 81, 85, 86, 93, 101, 103, 161, 168

F

Facility, 7, 8, 10, 14, 16, 17, 19, 21, 22, 24, 28, 30, 31, 34, 35,
37, 38, 40, 42, 43, 44, 45, 47, 49, 50, 52, 53, 55, 56, 57,
61, 62, 63, 64, 65, 68, 70, 71, 72, 73, 78, 79, 84, 86, 87,
91, 92, 95, 96, 98, 99, 103, 105, 106, 107, 108, 121, 124,
125, 126, 129, 130, 132, 133, 134, 135, 136, 137, 138,
139, 140, 141, 142, 143, 144, 145, 147, 154, 156, 157,
158, 159, 160, 163, 167, 171, 177, 181, 184, 188, 190,
191, 192, 193, 197, 200, 201, 202, 205
Father, 117
Food and Drug Administration (FDA), 6, 21, 24, 35, 46, 48,
49, 59, 63, 71, 73, 80, 85, 87, 88, 90, 99, 114, 115, 116,
118, 121, 133, 136, 143, 152, 158, 164, 165, 171, 175,
176, 178, 186, 188, 190, 202, 205
Foundation for the Accreditation of Cellular Therapy
(FACT), 6, 15, 16, 21, 32, 34, 43, 46, 60, 63, 65, 68, 73, 81,
82, 92, 93, 146, 185, 190, 197, 206, 216

G

Genetic disease, 58, 59, 112, 118, 120, 186, 187
Graft-versus-host disease (GVHD), 6, 194

H

Hematopoietic progenitor cells (HPC), 6, 8, 10, 11, 14, 64,
133, 165, 170
Hemoglobinopathy, 44, 47, 140, 165, 170, 171, 183, 204
Hepatitis B virus, 177, 178, 204
Hepatitis C virus, 204

HPC, Cord Blood, 14, 64, 133
Human immunodeficiency virus (HIV), 118, 119, 176, 177, 204
Human leukocyte antigen (HLA), 6, 11, 17, 25, 44, 48, 60, 112, 140, 149, 150, 151, 165, 174, 181, 184, 185, 196, 197, 198, 200, 204, 205
Human T cell lymphotropic virus (HTLV), 204, 205

I

Identification. See Unique identifier
Ineligible donor, 80, 190
Informed consent, 20, 43, 46, 62, 82, 85, 95, 96, 99, 106, 108, 109, 110, 111, 112, 113, 116, 127, 142, 143, 167, 168
Institutional Review Board (IRB), 7, 12, 62, 63, 147, 197
Interruption of operations, 29, 92
Inventory, 19, 20, 39, 41, 45, 50, 59, 66, 74, 79, 80, 81, 82, 83, 92, 93, 101, 103, 118, 119, 141, 143, 150, 156, 160, 166, 167, 168, 170, 173, 175, 182, 183, 193
ISBT 128, 12, 17, 63, 64, 65, 201

L

Labeling, 8, 12, 13, 14, 15, 19, 29, 34, 44, 47, 61, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 98, 102, 104, 107, 118, 119, 124, 125, 126, 129, 140, 142, 143, 145, 148, 154, 155, 166, 168, 178, 189, 191, 192, 200, 201
Labels, 8, 12, 13, 27, 28, 50, 51, 53, 61, 63, 64, 65, 66, 67, 68, 69, 71, 72, 73, 74, 102, 118, 125, 126, 143, 189, 200, 201
bar-coding, 68
biohazard. See Biohazard
partial, 13, 22, 68, 74, 143, 200
warning, 72, 73, 139, 200
Linkage, 12, 28, 32, 33, 40, 43, 46, 68, 69, 70, 71, 76, 77, 79, 107, 112, 114, 124, 125
Liquid nitrogen, 50, 69, 88, 138, 139, 141, 150, 154, 155, 157, 158, 159, 160, 161, 162, 163, 192

M

Manipulation, 12, 13, 14, 21, 48, 63, 71, 147, 148, 164, 165, 190
Marrow, 7, 11, 14, 190
Microbial culture, 20, 44, 47, 140, 156, 161, 171, 172, 173, 186, 204
Monitoring, 13, 15, 42, 45, 49, 50, 57, 61, 62, 79, 81, 90, 96, 101, 102, 108, 127, 128, 132, 136, 139, 141, 142, 146, 153, 158, 159, 161, 169, 196
Mother, 10, 12, 13, 16, 40, 44, 46, 47, 59, 61, 71, 97, 98, 101, 102, 106, 108, 109, 110, 111, 112, 113, 114, 116, 117, 118, 120, 121, 122, 124, 125, 152, 156, 167, 174, 176, 177, 187

birth, 13, 117, 120, 121, 152
egg, 13, 116, 117, 119, 152, 187
genetic, 13, 109, 116, 120, 121, 152
surrogate, 10, 13, 109, 116, 118

N

NetCord, 15, 16, 21, 43, 81, 82, 93, 185, 197, 206
Nonconforming CB unit, 13, 39, 44, 47, 59, 60, 82, 107, 113, 140, 164, 166, 184
Nucleated red blood cell count, 170

O

Operations, 8, 15, 19, 22, 24, 29, 42, 43, 50, 55, 56, 67, 68, 76, 78, 91, 92, 93, 94, 105, 108, 133, 134, 135, 139, 141, 182, 196
Organization, 6, 12, 13, 15, 20, 25, 38, 60, 63, 65, 85, 88, 133, 182
Outcome, 13, 20, 23, 24, 29, 30, 33, 38, 40, 41, 42, 43, 44, 49, 62, 67, 84, 86, 88, 144, 146, 169, 180, 194, 195, 196

P

Personnel, 9, 14, 15, 16, 17, 22, 23, 24, 25, 26, 28, 29, 30, 32, 33, 34, 43, 46, 49, 50, 51, 52, 53, 54, 56, 57, 58, 60, 61, 65, 68, 69, 72, 73, 82, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 95, 96, 97, 98, 99, 100, 101, 103, 104, 105, 106, 107, 108, 109, 110, 112, 123, 126, 127, 134, 135, 136, 137, 138, 139, 140, 141, 142, 144, 145, 148, 153, 155, 160, 162, 163, 166, 168, 169, 176, 181, 190, 193, 196, 197, 208
Policy, 8, 13, 19, 25, 26, 27, 28, 29, 30, 31, 35, 38, 40, 41, 42, 43, 45, 46, 50, 51, 52, 53, 54, 55, 56, 58, 59, 60, 61, 65, 72, 75, 81, 85, 86, 87, 89, 90, 92, 95, 98, 99, 105, 106, 112, 113, 114, 115, 118, 120, 122, 123, 124, 132, 135, 137, 139, 140, 142, 143, 145, 147, 148, 150, 153, 154, 160, 161, 163, 164, 166, 167, 171, 174, 175, 176, 177, 178, 181, 182, 183, 193, 194, 195, 196, 205
Potency, 8, 10, 11, 13, 16, 40, 81, 93, 125, 136, 139, 140, 143, 144, 145, 146, 149, 150, 151, 152, 153, 154, 155, 159, 160, 161, 165, 168, 169, 170, 171, 181, 188, 204, 205, 206
Process control, 14, 37, 44, 47, 56, 107, 140, 144
Processing, 7, 8, 9, 10, 12, 13, 14, 16, 20, 21, 22, 23, 24, 25, 29, 30, 31, 32, 34, 37, 39, 40, 42, 44, 47, 50, 53, 56, 57, 61, 62, 64, 65, 67, 69, 71, 72, 73, 74, 76, 78, 79, 81, 83, 85, 86, 87, 91, 92, 95, 99, 106, 107, 110, 121, 124, 126, 128, 129, 130, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 152, 153, 154, 155, 158, 159, 160, 161, 167, 168, 169, 170, 171, 172, 173, 175, 181, 183, 187, 188, 190, 191, 196, 197, 200, 204, 205, 206, 208

Processing facility, 7, 10, 21, 22, 24, 25, 37, 42, 44, 47, 53, 56, 57, 61, 62, 64, 65, 71, 72, 73, 79, 86, 92, 95, 99, 106, 107, 121, 124, 126, 129, 130, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 154, 158, 159, 167, 169, 171, 172, 190, 191, 196, 200
Product tracking, 17, 28, 31, 32, 34, 40, 43, 55, 57, 62, 76, 79, 103, 117, 124, 129, 159, 192, 193, 194
Proficiency, 14, 169

Q

Qualification, 14, 22, 25, 26, 35, 36, 37, 38, 43, 44, 47, 48, 49, 75, 79, 80, 86, 108, 127, 141, 148, 161, 181, 197
Quality assessment, 14, 15, 23, 35
Quality assurance, 14, 164
Quality control, 15, 16, 34, 37, 40, 51, 76, 77, 84, 114, 151, 166, 168, 169
Quality management, 7, 15, 19, 23, 30, 41, 42, 56, 196
Quality Management Plan, 15, 24, 25, 26, 27, 29, 30, 31, 35, 37, 38, 40, 41, 42, 51, 61, 62, 127, 147
Quality unit, 15, 22, 23, 24, 30, 32, 33, 35, 38, 39, 41, 42, 51, 59, 67, 144, 147, 155, 156, 157, 169, 187, 188, 189, 196, 197
Quarantine, 15, 31, 47, 66, 67, 68, 73, 80, 83, 119, 140, 155, 156, 157, 158, 160, 167, 173, 177, 178, 202

R

Reagent, 7, 14, 15, 19, 33, 34, 35, 36, 37, 38, 56, 61, 78, 79, 80, 86, 93, 94, 96, 97, 100, 101, 102, 103, 104, 123, 124, 134, 137, 145, 147, 148, 155, 166, 168, 169, 173, 175
Recipient, 7, 9, 11, 14, 15, 16, 17, 20, 26, 40, 41, 42, 44, 48, 57, 59, 60, 61, 72, 79, 97, 114, 115, 117, 124, 143, 144, 166, 167, 168, 169, 170, 173, 175, 176, 181, 182, 185, 187, 189, 190, 191, 192, 200
Records, 9, 11, 15, 19, 24, 27, 28, 29, 30, 31, 32, 33, 37, 40, 41, 42, 43, 44, 46, 47, 49, 56, 57, 58, 59, 61, 68, 69, 70, 71, 72, 73, 75, 76, 77, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 96, 99, 101, 104, 105, 107, 111, 112, 115, 118, 120, 123, 124, 126, 127, 128, 129, 134, 136, 137, 140, 141, 145, 147, 148, 155, 156, 157, 158, 159, 160, 161, 162, 166, 168, 170, 175, 177, 180, 182, 183, 184, 186, 188, 190, 191, 192, 193, 202
Registry, 15, 21, 22, 24, 25, 31, 34, 35, 41, 48, 56, 61, 82, 85, 93, 94, 113, 163, 164, 170, 172, 177, 181, 182, 183, 184, 185, 188, 191, 193, 198
Release, 7, 9, 10, 15, 16, 20, 21, 22, 23, 24, 30, 32, 44, 47, 48, 49, 57, 58, 67, 80, 81, 85, 86, 87, 93, 112, 113, 114, 117, 118, 134, 139, 140, 142, 143, 144, 155, 156, 157, 160, 161, 163, 164, 166, 168, 170, 173, 174, 177, 178, 180, 181, 182, 183, 184, 185, 186, 187, 188, 190, 193, 194, 195, 196, 197, 198, 202, 204, 205, 206

Reservation, 7, 9, 15, 20, 21, 30, 32, 44, 48, 57, 87, 180, 181, 182, 197
Rh type, 165, 200

S

Safety, 8, 10, 11, 16, 19, 24, 25, 40, 41, 43, 45, 49, 50, 53, 54, 55, 56, 57, 74, 84, 87, 88, 93, 101, 102, 104, 106, 107, 108, 114, 115, 121, 122, 126, 134, 135, 136, 137, 138, 139, 140, 141, 145, 154, 165, 168, 175, 183, 188, 196
Sample, 16, 39, 44, 46, 47, 60, 61, 66, 67, 68, 70, 71, 74, 75, 80, 83, 93, 99, 100, 102, 107, 112, 120, 121, 124, 125, 129, 132, 140, 142, 144, 147, 148, 149, 150, 151, 152, 154, 155, 157, 159, 162, 163, 166, 169, 170, 171, 172, 175, 176, 177, 178, 184, 204, 205
Sanitation. See Cleaning
Segment, 9, 17, 48, 70, 83, 93, 149, 150, 151, 154, 157, 159, 160, 165, 184, 185, 189, 204, 205, 206
Selection, 7, 9, 13, 16, 20, 21, 24, 26, 30, 32, 35, 44, 48, 57, 60, 61, 78, 86, 87, 96, 98, 115, 164, 170, 174, 175, 180, 181, 182, 184, 185, 187, 197, 205
Shipping, 9, 16, 41, 44, 47, 50, 57, 73, 83, 95, 97, 98, 99, 100, 102, 104, 105, 107, 124, 126, 127, 128, 129, 130, 141, 142, 154, 180, 184, 187, 188, 191, 192, 193, 200, 201, 202
Specifications, 8, 11, 14, 37, 38, 39, 44, 47, 48, 75, 76, 80, 107, 115, 124, 140, 144, 145, 150, 164, 166, 168, 205, 206
Standard Operating Procedure, 8, 15, 16, 17, 19, 25, 26, 27, 28, 29, 30, 31, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 45, 46, 50, 51, 52, 53, 54, 55, 56, 58, 59, 61, 68, 72, 74, 76, 77, 79, 83, 84, 88, 90, 91, 93, 95, 98, 99, 101, 105, 106, 115, 118, 120, 121, 122, 126, 127, 132, 136, 137, 139, 140, 142, 143, 144, 145, 147, 148, 153, 155, 156, 158, 160, 174, 175, 176, 177, 178, 181, 182, 183, 193, 194, 196
Sterility, 7, 8, 15, 16, 34, 36, 55, 62, 75, 78, 79, 80, 83, 99, 104, 113, 122, 123, 124, 128, 134, 135, 139, 145, 146, 148, 154, 155, 156, 157, 158, 159, 160, 161, 165, 172, 173, 174
Storage, 7, 9, 11, 13, 14, 16, 20, 21, 22, 24, 25, 28, 29, 30, 31, 32, 40, 44, 46, 47, 48, 49, 50, 56, 57, 58, 61, 66, 67, 68, 69, 70, 73, 74, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 93, 96, 98, 99, 100, 101, 102, 104, 107, 110, 111, 112, 113, 117, 119, 120, 124, 125, 126, 127, 132, 134, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 149, 150, 151, 152, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 167, 169, 173, 174, 177, 178, 181, 186, 187, 188, 189, 196, 197, 200, 205, 206
Supplies, 13, 14, 19, 35, 37, 38, 48, 52, 56, 61, 78, 79, 80, 86, 93, 94, 96, 97, 98, 99, 100, 101, 102, 103, 104, 124, 134, 137, 148

T

Temperature, 10, 33, 37, 46, 47, 79, 81, 98, 100, 101, 102, 122, 124, 125, 126, 127, 128, 136, 139, 142, 144, 146, 147, 151, 152, 153, 154, 158, 159, 160, 161, 162, 163, 192, 193, 200

Testing, 7, 9, 11, 12, 13, 14, 15, 16, 20, 21, 24, 25, 30, 31, 32, 34, 37, 38, 39, 43, 44, 46, 47, 48, 57, 58, 59, 60, 61, 68, 70, 72, 73, 76, 83, 85, 86, 87, 91, 93, 107, 110, 111, 112, 114, 117, 118, 119, 120, 121, 125, 128, 132, 134, 140, 142, 149, 150, 151, 156, 157, 158, 159, 160, 161, 164, 165, 166, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 181, 183, 184, 185, 186, 187, 188, 189, 190, 191, 196, 197, 198, 202, 204, 205, 206

Thawing, 41, 64, 80, 144, 146, 147, 153, 160, 161, 166, 169, 188, 189, 190, 191, 194, 204, 205, 206

Total Nucleated Cell (TNC), 7, 17, 128, 152, 153, 165, 166, 168, 170

Trace, 12, 17, 29, 40, 43, 57, 61, 69, 70, 76, 77, 87, 100, 103, 124, 153, 168, 171, 177, 189, 192

Transplant center. *See* Clinical Program

Transport, 9, 10, 17, 33, 41, 44, 47, 50, 57, 70, 74, 80, 81, 83, 95, 98, 99, 102, 104, 107, 124, 126, 127, 128, 129, 141, 146, 154, 159, 167, 180, 184, 187, 188, 191, 192, 193, 200

Trypanosoma cruzi, 205

U

Unique identifier, 17, 28, 70, 71, 74, 80, 124, 200

V

Validation, 17, 27, 35, 36, 37, 38, 39, 40, 43, 46, 65, 66, 67, 69, 71, 74, 75, 79, 81, 88, 89, 90, 91, 93, 100, 101, 102, 114, 122, 123, 125, 127, 128, 142, 143, 144, 146, 148, 149, 150, 151, 152, 153, 154, 155, 158, 159, 160, 161, 162, 164, 166, 169, 170, 171, 172, 173, 174, 175, 182, 184, 188, 191, 192, 193, 204, 205, 206

Variance, 17, 31, 32, 35, 43, 187

Verification, 14, 17, 27, 30, 31, 34, 37, 40, 42, 43, 44, 45, 48, 49, 64, 67, 68, 69, 73, 78, 80, 81, 82, 83, 86, 87, 88, 89, 90, 91, 93, 100, 101, 104, 107, 108, 109, 115, 118, 122, 124, 125, 127, 128, 140, 142, 143, 144, 146, 148, 150, 161, 162, 169, 181, 184, 185, 193, 198, 204, 205, 206

Viability, 10, 16, 17, 37, 39, 40, 48, 62, 75, 78, 81, 83, 100, 122, 123, 125, 127, 143, 144, 145, 148, 149, 150, 151, 152, 153, 154, 159, 160, 168, 169, 170, 181, 184, 204, 206

W

Warming, 17, 20, 31, 102, 159, 160, 163

Written agreement. *See* Agreement

This page intentionally left blank.

FACT Accreditation Office

University of Nebraska Medical Center
986065 Nebraska Medical Center
Omaha, NE 68198-6065

Phone: (402) 559-1950

Fax: (402) 559-1951