

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



**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.

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INTRODUCTION

The major objective of the sixth edition *NetCord-FACT International Standards for Cord Blood Collection, Banking, and Release for Administration* (the "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.

These Standards are effective on September 29, 2016. All accredited Cord Blood Banks are expected to be in compliance with these Standards by that date.

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.

TERMINOLOGY, TENETS, ABBREVIATIONS, AND DEFINITIONS

PART A

- A1 Terminology
- A2 Tenets
- A3 Abbreviations
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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 that 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.icbba.org> > Subject Area > Cellular Therapy > Standard Terminology.*

CORD BLOOD BANK OPERATIONAL STANDARDS

PART B

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PART B: CORD BLOOD BANK OPERATIONAL STANDARDS

B1: GENERAL REQUIREMENTS

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.

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.

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.

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.

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

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

B2: QUALITY MANAGEMENT

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.

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

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.

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.

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.

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:

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.

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.

B2.5.3 A system that provides consistent training programs.

B2.5.4 A description of minimum trainer qualifications.

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.
- 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.
- B2.7.5 Assignment of a numeric or alphanumeric identifier and title to each document and document version regulated within the system.
- 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.
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- 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.
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- 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.
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- B2.10 The QM Plan shall summarize and reference policies and Standard Operating Procedures for maintaining confidentiality.

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- 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.

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- 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:
- 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.
 - 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.
 - 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.
 - 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.
- 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.
 - 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.
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- 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.
 - B2.13.2 Qualification studies shall include verification that suppliers of critical supplies, reagents, services, and equipment comply with Applicable Law and these Standards.
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- B2.14 The QM Plan shall summarize and reference policies and Standard Operating Procedures for validation of critical procedures of the CBB.
 - B2.14.1 The Quality Unit and CBB Director or designee shall determine which procedures are considered critical.
 - 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.

- 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.
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- 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.
- B2.15.2 Documentation of all facilities involved in each stage of CB unit manufacturing shall be maintained.
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- 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.
- 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.
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- 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.
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- B2.18 The Quality Unit Manager shall review and report on quality management activities, at a minimum, quarterly.
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- 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.

B3: POLICIES AND STANDARD OPERATING PROCEDURES

- 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:
- B3.1.1 Donor recruitment and education.
 - B3.1.2 Maternal screening and testing (including interpretation and acceptable results).
 - 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.
 - 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.
- 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.
- 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.
- B3.1.26 For allogeneic use, verification that the infant donor and recipient are different individuals in the case of complete HLA matches.
- B3.1.27 CB unit recall, including a description of actions to be taken, responsible personnel, and notification of appropriate regulatory agencies.
- 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.
- 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.
- 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.
- B3.1.42 Disposal of CB units.

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- 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.
 - 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.
- 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:
- 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.
 - B3.3.4 A stepwise description of the procedure.
 - B3.3.5 Acceptable end-points and the expected range of results, if applicable.
 - B3.3.6 Reference to other Standard Operating Procedures or policies required to perform the procedure.
 - B3.3.7 A reference section listing appropriate literature, if applicable.
 - B3.3.8 Reference to the current version of worksheets, forms, reports, and labels, where applicable.

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

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.

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.

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

B4: FACILITIES AND SAFETY

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.

B5: CORD BLOOD BANK OPERATIONS

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.
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B6: CODING AND LABELING OF CORD BLOOD UNITS

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.
 - B6.1.2 If coding and labeling technologies have not yet been implemented, the CBB shall be actively implementing ISBT 128.
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B6.2 Label Controls.

- B6.2.1 A system for label version control shall be employed.
 - B6.2.1.1 Previous versions of labels shall be archived indefinitely.
- B6.2.2 A system for label reconciliation shall be employed.
- B6.2.3 The label shall be validated as reliable for storage under the conditions in use.
- 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.
 - 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.
- 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.

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

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.

- 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.
- 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.
- 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.
- 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.

B7: EQUIPMENT

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.

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.

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.

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.

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.

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

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

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.

B9: INVENTORY MANAGEMENT

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.

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.

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.

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- 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.
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B10: INVENTORY TRANSFER

- 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.
-
- 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.
 - 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.
 - 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.
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- 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.
 - 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

- 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.
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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:

B11.5.1 Infant donor and parental records.

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

B11.5.3 QM records.

B11.5.4 Personnel records.

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

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.

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.
- 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.
- 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:
 - 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.
 - 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.
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B12: INTERRUPTION OF OPERATIONS AT ESTABLISHED SITES

- 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.
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- 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.
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- 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.
 - 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.
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- B12.4 Prior to the reestablishment of either CB collection or banking, as applicable, the following at a minimum shall be documented:
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- 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.
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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.

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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

- C1.1 These Standards shall apply to all CB activities.
-
- 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.
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- C1.3 The CB Collection Sites shall have processes to prevent the introduction, transmission, or spread of communicable disease.
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- C1.4 There shall be adequate space for the performance of the collection procedure.
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- 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.
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- 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.
 - 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.
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- 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.

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.

C1.10 Identity of supplies and reagents including manufacturer, lot number, and expiration date shall be documented for each collection.

C2: CORD BLOOD COLLECTION PERSONNEL REQUIREMENTS

C2.1 All CB collection personnel shall comply with these Standards.

C2.2 All CB collection personnel shall have a defined line of communication with relevant CBB personnel.

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.
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C3: POLICIES AND STANDARD OPERATING PROCEDURES

- 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:
 - C3.1.1 Donor recruitment and education.
 - C3.1.2 Maternal and infant donor screening.
 - C3.1.3 Informed consent.
 - C3.1.4 Suitability assessment of maternal and infant donor.
 - C3.1.5 Interaction between the CB Collection Site and the CBB.
 - C3.1.6 Documentation of infant donor health at birth.
 - 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.
 - 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.
 - 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.
 - C3.1.28 Disposal of a CB unit.
-

C4: INFORMED CONSENT

- 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.

- 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.
- 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.
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- C4.2 All aspects of participation in CB donation shall be discussed with the mother in a language and with terms that she understands.
-
- 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.
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- C4.4 The mother shall have an opportunity to ask questions.
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- 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.
 - 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.
 - 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.
 - 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.
- 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.
- 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.
- 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

- 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.
 - 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.
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- C5.2 Maternal and infant donor screening shall include a medical history, review of medical records, and review of physical examination findings.
- 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.
 - 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.
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- 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.
 - C5.3.2 The history shall include at a minimum genetic history, malignant disease, and inherited disorders that may be transmissible to the recipient.
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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.
 - 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.
 - 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.
 - 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.
 - C5.4.7 There shall be screening for human transmissible spongiform encephalopathy, including Creutzfeldt-Jakob disease.
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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.
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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.

- 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.
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C6: CORD BLOOD COLLECTION

- 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.
 - 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.
 - C6.3.4 Methods for CB collection shall employ aseptic techniques.
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- 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.
 - C6.3.6 All supplies and reagents for CB collection that come into contact with the CB unit shall be sterile.
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C6.4 There shall be a unique numeric or alphanumeric identifier for the CB unit, associated samples, maternal samples, and associated documents.

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.

- C6.7.2 CB units shall be maintained in a temperature range validated to protect cell viability.

C6.8 The chain of custody of the CB unit shall be maintained from collection to receipt at the CBB.

C6.9 Records shall be maintained at the CBB of all reports of adverse events that occur during or immediately after CB collection.

C7: TRANSPORTATION AND SHIPPING OF UNMANIPULATED CORD BLOOD UNITS BETWEEN THE CORD BLOOD COLLECTION SITE AND THE CORD BLOOD PROCESSING FACILITY

C7.1 Transport and shipping of CB units shall be in compliance with Applicable Law.

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- 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.
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- 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.
-
- 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.
 - 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.
-
- 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.
-
- 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.

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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

D1.1 The CB Processing Facility shall be licensed, registered, or accredited as required by the appropriate governmental authorities for the activities performed.

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.

D1.3 The CB Processing Facility shall be secure in order to prevent the entrance of unauthorized personnel.

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.

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.

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.

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:

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.

D1.7.1.5 Latex allergy.

D1.7.1.6 Radiation safety, if applicable.

D1.7.1.7 Fire safety.

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.

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.

D1.7.5 Oxygen levels should be monitored wherever liquid nitrogen is in use.

D2: POLICIES AND STANDARD OPERATING PROCEDURES

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:

- 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.
- 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.
- 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

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.
-

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.
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- 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.
 - D3.2.4.1 Critical control points shall be identified and their specifications defined.
 - D3.2.4.2 Failure of the processing procedure to achieve specifications for critical control points shall be evaluated with appropriate action documented.
 - 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.
 - 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.
 - 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.
 - 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.
 - 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.
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- 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

- D4.1 At a minimum, the following samples shall be collected from the CB unit prior to cryopreservation:
- 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.
 - D4.1.1.1 The contents of each contiguous segment shall be representative of the CB unit.
 - 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.
 - 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.
 - 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.
 - D4.1.2.2 Reference samples used for purposes other than viability or potency analysis shall be stored at -70°C or colder.
 - D4.1.3 A minimum total volume of 3.6 mL of plasma from the CB unit divided into at least two (2) vials.
 - 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 μ g genomic DNA.

D4.2 At least one retention sample from the CB unit should be stored indefinitely.

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.

D5: CRYOPRESERVATION

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 $\geq 60\%$ after processing prior to cryopreservation.

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.

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.

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.

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.

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- 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.
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D6: CONDITIONS FOR STORAGE

- 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.
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- 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.
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- D6.3 Procedures to minimize the risk of microbial cross-contamination of CB units shall be defined and maintained.
-
- 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.
- D6.4.3 Records shall indicate when a CB unit was released from quarantine into permanent storage.
- 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.

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.

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.

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.

D7: MONITORING AND ALARM SYSTEMS

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.

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.

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- 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.
 - D7.4.5 Alarm parameters shall be set to allow staff sufficient time to salvage CB units and samples.
 - 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.
 - 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.
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D8: DISPOSITION

- 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.
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- D8.2 CB units shall meet the requirements outlined in the Specification Requirements table in Appendix V.
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- 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.
-

- 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.
 - D8.4.3 For related CB unit disposal:
 - D8.4.3.1 Disposal shall comply with the terms of disposal in the written agreement.
 - D8.4.3.2 Reasons for disposal and notification of the donor's family shall be documented.
-

D9: CORD BLOOD UNIT TESTING

- 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.

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.

D9.3 CB units shall be tested as outlined in the Testing Requirements table in Appendix IV.

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.

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.

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.

D9.3.3 HLA Class I and Class II typing shall be performed by DNA-based methods.

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

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.

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.

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.

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.

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.

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.

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

- 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.
 - 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.
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- E1.4 If the CBB utilizes a registry, the CBB shall use a validated process for uploading CB unit information to the registry.
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- 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.
-

E2: REVIEW OF CORD BLOOD UNIT RECORDS

- E2.1 The CBB shall have policies and Standard Operating Procedures for the comprehensive review of CB unit records, including at a minimum:
- 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.
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- E2.3 The nature of ineligible or nonconforming CB units shall be disclosed to the registry and/or the requesting party.
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E3: CORD BLOOD UNIT SELECTION AND RELEASE FOR ADMINISTRATION

- 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.

-
- 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.
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- 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:
- 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.
 - E3.3.2 For related CB units with positive microbial tests documented in the CB unit record, antimicrobial sensitivities.
 - 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.
 - 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.
 - 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.

- 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.
 - 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.
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E4: CORD BLOOD UNIT DISTRIBUTION TO A CLINICAL PROGRAM

- 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.
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- 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.
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- 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.
-
- 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.
-
- 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.

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.

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."

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

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.

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

- 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.

- 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.
-

E7: CLINICAL OUTCOME DATA

- 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.
- 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.

APPENDIX I

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 • Quality Program 	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.

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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 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.

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APPENDIX IV

TESTING REQUIREMENTS

Test	CB Samples						Maternal Samples
	Pre-processing	Post-processing prior to cryo-preservation	Any time prior to cryo-preservation	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)
Sterility	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.

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ACKNOWLEDGEMENTS

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