NetCord-FACT International Standards for Cord Blood Collection, Banking, and Release for Administration

Fourth Edition

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

Fourth Edition
January 2010

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 establishes additional requirements. Each Cord Blood Bank, facility, and individual should analyze its practices and procedures to determine whether additional standards apply. The Foundation for the Accreditation of Cellular Therapy and NetCord disclaim any responsibility for setting maximum standards and expressly do not represent or warrant that compliance with these Standards is an exclusive means of complying with the standard of care in the industry or community.

TABLE OF CONTENTS

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INTRODUCTION

The fourth edition of the *NetCord-FACT International Standards for Cord Blood Collection, Banking, and Release for Administration* (Standards) is a collaborative effort between NetCord and the Foundation for the Accreditation of Cellular Therapy (FACT). Founded in 1998, NetCord is the international cord blood banking arm of EuroCord, an international registry for the European Group for Blood and Marrow Transplantation (EBMT). The mission of NetCord is to promote high quality cord blood banking and clinical use of umbilical cord blood for allogeneic stem cell transplantation. FACT was founded in 1996 by its two parent organizations, the American Society for Blood and Marrow Transplantation (ASBMT) and the International Society for Cellular Therapy (ISCT). FACT's mission is to promote quality medical and laboratory practice of cellular therapy through its peer-developed standards and voluntary inspection and accreditation program.

The major objective of these Standards is to promote quality medical and laboratory practices throughout all phases of cord blood collection and banking to achieve consistent production of high quality placental and umbilical cord blood units for administration. The title of the Standards was updated with this fourth edition to specify that all phases of cord blood collection, banking, and release for administration are included, including donor management, collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, and distribution to clinical programs. 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 unit; 4) making the CB unit available for administration, either directly or through listing with a search registry; 5) the search and reservation process for selection of specific cord blood units; and 6) all transport or shipment of cord blood units, whether fresh or cryopreserved. Standards for the administration of cord blood cells, either allogeneic or autologous, are covered in the Clinical Program section of the *FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration.*

These Standards were developed by consensus, based on the best available evidence-based science to the greatest extent possible, placing emphasis on research findings related to 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 Standards Committee weighed the available evidence from preclinical studies and accepted scientific theory.

These Standards apply to cord blood units intended for unrelated allogeneic use and to units collected and stored for the directed use by a specific individual recipient or family member of the donor. Cord Blood Banks are not required to have any specific structure. Cord Blood Banks 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. These Standards place significant responsibility on the Cord Blood Bank Director and Medical Director for implementation of systems and processes that result in high quality cord blood units.

To be compliant with the Standards, Cord Blood Banks must maintain a comprehensive, properly documented Quality Management (QM) Program; use validated methods and qualified supplies, reagents, and equipment; and track the clinical outcomes of patients who receive cord blood units from that bank. In the previous edition, QM requirements were detailed in a separate section of the Standards. In the fourth edition, the QM standards have been integrated into the Cord Blood Bank Operational Standards section to emphasize the importance of including all phases of cord blood unit manufacturing in the QM Program. The QM standards have been realigned to reduce redundant

references to QM topics, yet still maintain the rigorous assurances of a QM Program that result in high-quality cord blood collection, banking, and release for administration. The QM standards are organized on a topical basis; operational quality control standards are relocated to the operational sections to which they pertain.

NetCord and FACT recognize the significant benefits of international standardization of coding and labeling in cellular therapy, and support the international efforts to implement *ISBT 128*, the international information standard for transfusion and transplantation. These Standards require the use of *ISBT 128* terminology as applicable. The product definitions in this edition of the Standards are consistent with the *ISBT 128* definitions at the time of publication; however, it is the Cord Blood Bank's responsibility to ensure use of the most current terminology as detailed in *ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions*, which can be found at http://www.iccbba.org/standardterminology.pdf. Cord Blood Banks utilizing bar codes should register with ICCBBA, Inc., the organization charged with the international maintenance of this database, to obtain the necessary documents, databases, product codes, and facility identifiers.

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 establishes additional requirements. Each Cord Blood Bank, facility, and individual should analyze its practices and procedures to determine whether additional standards apply. FACT and NetCord disclaim any responsibility for setting maximum standards and expressly do not represent or warrant that compliance with these Standards is an exclusive means of complying with the standard of care in the industry or community. In the event that a printed copy of the Standards differs from the version posted on the FACT website at www.factwebsite.org, the web version prevails. In the event of translation into a language other than English, the official version is the English version.

These Standards are effective on March 31, 2010. 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 the Standards. 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.

The inspection and accreditation process includes submission of written documents and an on-site inspection of the Cord Blood Bank, Cord Blood Collection Sites, Cord Blood Processing Facilities, and Storage Facilities. Depending on the number of Cord Blood Collection Sites associated with the Cord Blood Bank, all or a subset of the collection sites will be visited. The inspection team includes at least three inspectors and may include interpreters for Cord Blood Banks where English is not the primary language. The FACT-NetCord inspectorate consists of highly 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 Site Directors, and Cord Blood Processing Facility Directors. Cord blood inspectors must be affiliated with a FACT or FACT-NetCord accredited or applicant facility

and must be a member of ASBMT, ISCT, EBMT, ISCT-Europe, or NetCord. All inspectors must complete an inspector training course and participate in at least one inspection as a trainee inspector.

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/or NetCord Board of Directors. Accreditation may be suspended or terminated if a bank, site, or facility fails to comply with the Standards.

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PART A: TERMINOLOGY, ABBREVIATIONS, AND DEFINITIONS

A1 TERMINOLOGY

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

A2 ABBREVIATIONS

The following abbreviations are used in these Cord Blood Standards:

ABO	Major human blood group including erythrocyte antigens, A, B, O
C	Accompany
F	Affix
ASHI	American Society for Histocompatibility and Immunogenetics
T	Attach
°C	Degree Celsius
CB	Cord blood
CBB	Cord blood bank
CBC	Complete blood count (Full blood count)
CB unit	Cord blood unit
CFU	Colony forming unit
DNA	Deoxyribonucleic acid
EFI	European Federation for Immunogenetics
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	United States Food and Drug Administration
GVHD	Graft-versus-host disease
HLA	Human leukocyte antigen
HPC	Hematopoietic progenitor cell
IRB	Institutional Review Board
ISBT	International Society of Blood Transfusion
μg	Microgram
mL	Milliliter
QM	Quality Management
Rh	Human erythrocyte antigen, Rhesus
TNC	Total nucleated cell
USDA	United States Department of Agriculture
WMDA	World Marrow Donor Association

A3 DEFINITIONS

The following terms are used in this document with the following definitions:

Accompany (C): 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.

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

Allogeneic: Obtained from an infant donor and intended for infusion into a genetically distinct recipient.

Directed allogeneic: Collected and stored for use by an individual or family that is genetically related to the infant donor.

Unrelated allogeneic: Obtained from an infant donor and intended for administration into another individual who is not genetically related to the infant donor.

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, patients, or donors.

Attach (T): 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: 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.

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. The *Circular of Information for the Use of Cellular Therapy Products* is a jointly prepared document containing definitions; descriptions; indications and contraindications; and instructions for dosage, administration, storage, labeling, and documentation of cellular therapy products such as hematopoietic progenitor cells and other leukocytes that are minimally manipulated. The current *Circular of Information* can be found at www.factwebsite.org.

Clinical Program: An integrated medical team that administers cord blood units.

Colony forming unit (CFU): A clonogeneic 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.

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 infusion of a cord blood unit.

Confirmatory typing: A test performed on a second sample of a specific CB donation at the request of a Clinical Program to confirm the original typing and/or to reaffirm the identity of the CB donation.

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.

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 and/or umbilical cord vessels after the placenta has been delivered.

In utero: The collection of cord blood cells from the placental and/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 site 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. 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 without an ongoing documented agreement with a Cord Blood Bank where one or more cord blood units may be collected at the initiation of the infant donor's mother and/or family and with documentation that a licensed health care professional has agreed to perform the collection 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. HPC, Cord Blood is the proper name of a cord blood unit. 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.

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.

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

Cord Blood Bank Director: An individual with an earned doctoral degree in medicine or in a related scientific field, with training in immunogenetics of transplantation, basic or clinical immunology, immunohematology, basic or clinical hematology, transfusion medicine, blood or tissue banking, or cryobiology. The Cord Blood Bank Director has final responsibility for the Cord Blood Bank operations and its overall compliance with these Standards including all components of the Cord Blood Bank's policies and Standard Operating Procedures. The Cord Blood Bank Director shall participate regularly in educational activities related to the field of cord blood banking and/or cellular therapy product collection, processing, and transplantation.

Cord Blood Bank Medical Director: A licensed physician with training in hematopoietic cell transplantation or blood or tissue banking. This individual is responsible for donor recruitment, donor eligibility, the medical aspects of the cord blood collection procedures and of the Cord Blood Bank Processing Facilities; and compliance of the Cord Blood Collection Sites and Cord Blood Processing Facilities with these Standards. The Cord Blood Bank Medical Director shall participate regularly in educational activities related to the field of donor safety, cord blood banking, and/or cellular therapy product collection, processing, and transplantation. The Cord Blood Bank Medical Director may also serve as the Cord Blood Bank Director, Cord Blood Collection Site Director, and/or Cord Blood Processing Facility Director if appropriately credentialed.

Cord Blood Collection Site Director: A licensed health care professional who is responsible for communicating with the Cord Blood Bank Medical Director regarding operations at an individual Cord Blood Collection Site. The Cord Blood Collection Site Director shall participate regularly in educational activities related to the field of donor safety, cord blood banking and/or cellular therapy product collection, processing, and transplantation. The Cord Blood Bank Medical Director may serve the function of the Cord Blood Collection Site Director and need not be licensed in the jurisdiction of the cord blood collection or be on the staff of the Cord Blood Collection Site.

Cord Blood Processing Facility Director: An individual with a relevant doctoral degree, qualified by training or experience for the scope of activities carried out in the Cord Blood Processing Facility. The Cord Blood Processing Facility Director is responsible for all operational aspects of all procedures related to receipt, testing, processing, cryopreservation, storage, release for transport or shipment of cord blood units, and administrative operations of the Cord Blood Processing Facility, including compliance with these Standards. The Cord Blood Processing Facility Director shall participate regularly in educational activities related to the field of cord blood banking and/or cellular therapy product collection, processing, and transplantation. The Cord Blood Processing Facility Director may also serve as the Cord Blood Bank Director and/or Cord Blood Bank Medical Director if appropriately credentialed.

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 and/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 anonymously by a person with no known genetic relationship.

Directed donor: The infant whose cord blood is collected and stored for use by an individual or family that is genetically related to the donor. Directed donors can be related allogeneic or autologous donors.

Related donor: The infant whose cord blood is collected and stored for use by an individual or family that is genetically related to the donor.

Autologous donor: The infant whose cord blood is collected and stored for use by the donor.

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 infant donor and/or mother who meet(s) all donor screening and testing requirements related to transmission of communicable disease as defined by Applicable Law.

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.

Hematopoietic Progenitor Cells (HPC): Self-renewing and/or multi-potent stem cells capable of maturation into any of the hematopoietic lineages, lineage-restricted pluri-potent progenitor cells, and committed progenitor cells, regardless of tissue source (bone marrow, umbilical cord blood, peripheral blood, or other tissue source).

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

Indefinitely: A timeframe without a fixed or specified limit.

Ineligible: An infant donor and/or mother who does not meet all donor screening and testing requirements related to transmission of communicable disease as defined by Applicable Law.

Institutional Review Board 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.

Key personnel: Personnel with responsibilities that significantly affect the provision, safety, and/or quality of a service or product.

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/or the mother.

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

Manipulation: *Ex vivo* procedure(s) that selectively removes, enriches, expands, or functionally alters hematopoietic progenitor cells.

Maternal samples: Aliquots of cells, plasma, serum, or cellular material from the blood of the mother that can be used for testing.

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.

NetCord: The international organization of cord blood banks that meet defined membership requirements of the International NetCord Foundation, established to promote high quality cord blood banking and clinical use of umbilical cord blood for allogeneic stem cell transplantation.

Nonconforming cord blood unit: Any cord blood unit that does not completely meet the requirements specified by these Standards, the Cord Blood Bank, and/or the requirements for donor eligibility as defined by 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 defines the scope of an organization, explains how the goals of the organization will be achieved, and/or serves as a means by which authority can be delegated.

Positive selection: The manipulation of 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. 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: Umbilical cord blood and/or placental blood collected as a source of hematopoietic progenitor cells.

TC, Cord Blood: Umbilical cord blood and/or placental blood collected as a source of nucleated cells intended for therapeutic use other than HPCs.

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

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

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

Qualification: The establishment of confidence that 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 (QC): 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 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 Management Supervisor: A qualified individual approved by the Cord Blood Bank Director to establish 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, or a designation within the cord blood unit record.

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

Reference samples: Aliquots of cells, plasma, serum, or cellular material from the cord blood unit, the umbilical cord, or the placenta that can be used to confirm the identity, HLA typing, or genetic or communicable disease information associated with a single cord blood unit. Such samples may or may not be contiguous segments.

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.

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

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 trained personnel at the distributing or receiving facility.

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

Significant warming event: Any event when a cryopreserved cord blood unit reaches -120^{o} C or warmer during the life of the cryopreserved cord blood unit.

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 and/or distribution.

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

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

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

Transplantation: The infusion of allogeneic 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 trained personnel at the transporting or receiving facility.

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

Unique Identifier: A numeric or alphanumeric sequence used to designate a 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 cord blood unit 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. A process is validated by establishing, by objective evidence, that the process consistently produces a cord blood unit meeting its predetermined specifications.

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.

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

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

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PART B: CORD BLOOD BANK OPERATIONAL STANDARDS

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

PART B: CORD BLOOD BANK OPERATIONAL STANDARDS

B1 GENERAL REQUIREMENTS

B1.1 The Cord Blood Bank (CBB) shall consist of an integrated team, under a single CBB Director, 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 registered and/or accredited with the appropriate governmental authority for the activities performed.

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

B1.3.1 If the CBB utilizes a registry to deliver services related to the listing, search, selection, reservation, release, and/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, and/or any other aspect of banking, the responsibility of each entity shall be clearly documented.

B1.4.1 Each participating entity shall meet these Standards.

B1.5 There shall be a CBB Director, a CBB Medical Director, a CB Collection Site Director, a CB Processing Facility Director, and a Quality Management (QM) Supervisor.

B1.5.1 The CBB Director shall have an earned doctoral degree in medicine or in a related scientific field, with training in immunogenetics of transplantation, basic or clinical immunology, immunohematology, basic or clinical hematology, transfusion medicine, blood or tissue banking, or cryobiology. The CBB Director has final responsibility for the CBB operations and its overall compliance with these Standards, including all components of the CBB's policies and Standard Operating Procedures. The CBB Director shall participate regularly in educational activities related to the field of CB banking and/or cellular therapy product collection, processing, and transplantation.

B1.5.1.1 If the CBB Director does not have specific training and expertise in HLA, the CBB shall ensure HLA expertise is available and utilized by the CBB.

B1.5.2 The CBB Medical Director shall be a licensed physician with training in hematopoietic cell transplantation or blood or tissue banking. This individual is responsible for donor recruitment, donor eligibility, the medical aspects of the CB collection procedures and the CB Processing Facilities, and compliance of the CB Collection Sites and CB Processing Facilities with these Standards. The CBB Medical Director shall participate regularly in educational activities related to the field of donor safety, CB banking, and/or cellular therapy product collection, processing, and transplantation.

B1.5.2.1 The CBB Medical Director may also serve as the CBB Director, CB Collection Site Director, and/or CB Processing Facility Director if appropriately credentialed.

B1.5.3 The CB Collection Site Director shall be a licensed health care professional who is responsible for communicating with the CBB Medical Director regarding operations at an individual CB Collection Site. The CB Collection Site Director shall participate regularly in educational activities related to the field of donor safety, CB banking, and/or cellular therapy product collection, processing, and transplantation.

B1.5.3.1 The CBB Medical Director may serve the function of the CB Collection Site Director and need not be licensed in the jurisdiction of the CB collection or be on the staff of the CB Collection Site.

B1.5.4 The CB Processing Facility Director shall be an individual with a relevant doctoral degree, qualified by training or experience for the scope of activities carried out in the CB Processing Facility. The CB Processing Facility Director is responsible for 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. The CB Processing Facility Director shall participate regularly in educational activities related to the field of CB banking and/or cellular therapy product collection, processing, and transplantation.

B1.5.4.1 The CB Processing Facility Director may also serve as the CBB Director and/or CBB Medical Director if appropriately credentialed.

B1.5.5 The QM Supervisor shall be an individual with relevant training in QM and approved by the CBB Director to establish and maintain systems to review, modify as necessary, approve, and implement all Standard Operating Procedures related to QM and to monitor compliance with these Standards.

B1.5.5.1 The QM Supervisor shall be a different individual from the CBB Director, CBB Medical Director, CB Collection Site Director, and the CB Processing Facility Director.

B1.5.5.2 The QM Supervisor shall not have oversight of his/her own work if this person also performs other tasks in the CBB.

B1.5.5.3 The QM Supervisor shall participate regularly in educational activities related to the field of QM, CB banking, and/or cellular therapy product collection, processing, and transplantation.

B1.5.6 The CBB shall have adequate staff for its operations.

B1.5.6.1 Qualifications, training, continuing education, and continued competency for the performance of all assigned operations shall be documented for all staff.

B2 QUALITY MANAGEMENT

B2.1 The CBB shall establish and maintain a QM Program that includes all key CBB functions including donor management, collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, and distribution.

B2.1.1 The CBB shall establish and maintain a written QM Plan that describes the QM Program.

B2.1.2 The CBB Director shall be responsible for the QM Plan.

B2.1.3 The QM Supervisor shall report on the performance of the QM Program on an annual basis, at a minimum.

B2.2 The QM Plan shall document the relationship and interaction among all participating facilities and services, including, at a minimum, CB Collection Sites, CB Processing Facilities, testing laboratories, storage facilities, and registries.

B2.2.1 The QM Plan shall include, or summarize and reference, an organizational chart of key personnel, functions, and interactions within the CBB, the CB Collection Sites, and the CB Processing Facility.

B2.3 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for development and implementation of written agreements with external parties whose services impact the CB unit.

B2.3.1 Agreements shall include the responsibility of the external party performing any relevant aspect of CB collection, banking, or release for administration to comply with Applicable Law, these Standards, and the requirements of other applicable accrediting agencies.

B2.4 The QM Plan shall include, or summarize and reference, personnel requirements for each position in the CBB. Personnel requirements shall include at a minimum:

B2.4.1 Current position description for each staff member.

B2.4.2 A system to document for each staff member:

B2.4.2.1 Initial qualifications.

B2.4.2.2 Orientation.

B2.4.2.3 Initial training.

B2.4.2.4 Competency for each function performed.

B2.4.2.5 Continued competency at least annually.

B2.4.2.6 Continued education.

B2.4.2.7 Training on each procedure performed and retraining as necessary.

B2.4.3 Trainer and training requirements for each position in the CBB, including at a minimum:

B2.4.3.1 A policy and/or Standard Operating Procedure for personnel training and competency assessment.

B2.4.3.2 A system to ensure consistent training programs.

B2.4.3.3 A description of minimal trainer qualifications.

B2.4.4 Records of the signature, initials, and inclusive dates of employment for each staff member responsible for signing documents related to the CB unit.

B2.4.5 Documentation of who performs each step from collection to final disposition of the CB unit.

B2.5 The QM Plan shall include, or summarize and reference, a system for document control. The document control system shall include the following elements at a minimum:

B2.5.1 Definition and current listing of all critical documents that shall comply with the document control system requirements. Controlled documents shall include at a minimum:

B2.5.1.1 Standard Operating Procedures, policies, and protocols.

B2.5.1.2 Worksheets.

B2.5.1.3 Forms.

B2.5.1.4 Labels.

B2.5.1.5 Educational, promotional, and recruitment materials.

B2.5.2 Assignment of a numeric or alphanumeric identifier to each document and document version regulated within the system.

B2.5.3 A procedure for document approval, including the approval date, signature of approving individual(s), and the effective date.

B2.5.4 A procedure for document distribution to relevant personnel, including written confirmation that relevant personnel have received and read the document.

B2.5.5 A system for document change control that includes description of the change, signature of approving individual(s), approval date, and effective date.

B2.5.5.1 There shall be a system to ensure that controlled documents cannot undergo accidental or unauthorized modification.

B2.5.6 A system for document creation, assembly, review, storage, archival, retention, and retrieval.

B2.5.6.1 There shall be a system for the retraction of obsolete documents to prevent unintended use.

B2.5.6.2 Records of archived Standard Operating Procedures, protocols, and labels, in their historical sequence including inclusive dates of use, shall be maintained indefinitely.

B2.6 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for establishing and maintaining clearly written policies and Standard Operating Procedures that are precise and unambiguous and address all aspects of the operation.

B2.6.1 There shall be a Standard Operating Procedure for preparation, approval, implementation, and revision of Standard Operating Procedures.

B2.6.2 All policies and Standard Operating Procedures shall comply with these Standards.

B2.6.3 Copies of the policies and Standard Operating Procedures of the CBB relevant to the processes being performed shall be available to the CBB personnel at all times.

B2.6.4 The CBB shall maintain a detailed Standard Operating Procedures Manual. The Standard Operating Procedures Manual shall include at a minimum:

B2.6.4.1 A standardized format for procedures, including worksheets, reports, and forms.

B2.6.4.2 A standardized system of numbering.

B2.6.4.3 A standardized system of denoting the date each procedure became effective and when it was archived, if applicable.

B2.6.5 Each individual Standard Operating Procedure shall include:

B2.6.5.1 An appropriate title.

B2.6.5.2 A clearly written description of the objective.

B2.6.5.3 The personnel responsible for its execution.

B2.6.5.4 A description of the facility, equipment, and supplies required.

B2.6.5.5 A stepwise description of the procedure.

B2.6.5.6 Acceptable end-points and the expected range of results, if applicable.

B2.6.5.7 A reference to other Standard Operating Procedures or policies required to perform the procedure.

B2.6.5.8 A reference section listing appropriate literature, if applicable.

B2.6.5.9 A copy of current worksheets, forms, reports, and labels, where applicable.

B2.6.5.10 The date(s) and the approval signature of the CBB Director prior to implementation.

B2.6.5.11 The date of review or revision and the approval signature of the CBB Director or designee upon procedural modifications and at least every two years after implementation.

B2.6.6 There shall be policies and Standard Operating Procedures to cover the following CBB operations:

B2.6.6.1 Donor recruitment.

B2.6.6.2 Maternal screening and testing (including interpretation and acceptable results).

B2.6.6.3 Informed consent.

B2.6.6.4 Donor eligibility criteria and determination.

B2.6.6.5 Documentation of infant donor health at birth.

B2.6.6.6 Infant donor screening (including interpretation and acceptable results).

B2.6.6.7 Collection of CB, reference samples, and maternal samples.

B2.6.6.8 Storage of CB units, reference samples, maternal samples, and documentation.

B2.6.6.9 Transport and shipping of the CB unit, reference samples, maternal samples, and documentation to the CB Processing Facility.

B2.6.6.10 Labeling of the CB unit, reference samples, maternal samples, and associated documents.

B2.6.6.11 CB unit acceptance criteria, processing, cryopreservation, and storage.

B2.6.6.12 Process control, including product specifications and nonconforming products.

B2.6.6.13 Storage of reference samples and maternal samples for testing.

B2.6.6.14 Communicable disease testing, microbial cultures, HLA typing, hemoglobinopathy testing, and other testing. Acceptance criteria for test results shall be described.

B2.6.6.15 Notification of mothers or their responsible physicians and governmental agencies, when required, of positive or indeterminate communicable disease and/or genetic test results.

B2.6.6.16 Criteria for qualification and listing of CB units available for search and administration, including nonconforming CB units.

B2.6.6.17 Listing, search, selection, reservation, release, and distribution of CB units.

B2.6.6.18 Verification of confirmatory HLA typing of the CB unit.

B2.6.6.19 Verification that the infant donor and recipient are different individuals in the case of complete HLA matches.

B2.6.6.20 Collection and analysis of transplant outcome data.

B2.6.6.21 Discard and disposal of CB units.

B2.6.6.22 Electronic record entry, verification, and revision.

B2.6.6.23 Data management.

B2.6.6.24 CB unit records.

B2.6.6.25 CB unit disposition.

B2.6.6.26 Recipient follow-up.

B2.6.6.27 Facility management including supplies, maintenance and monitoring of equipment, cleaning and sanitation procedures, and disposal of medical and biohazardous waste.

B2.6.6.28 Emergency and safety procedures.

B2.6.6.29 Biological, chemical, and radiation safety.

B2.6.6.30 Disaster plan, including CBB-specific issues.

B2.6.7 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.

B2.7 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures to support management of electronic record systems and electronic records and to maintain pertinent electronic records, if applicable.

B2.7.1 The QM Plan shall include policies and Standard Operating Procedures to ensure continuous operations in the event that the electronic record system ceases to function, including a plan for data backup and to ensure compliance with Applicable Law.

B2.8 The QM Plan shall include, or summarize and reference, a system to maintain confidentiality.

B2.9 The QM Plan shall include, or summarize and reference, policies, Standard Operating Procedures, and a schedule for conducting audits of key CBB functions annually at a minimum.

B2.9.1 Key functions shall include donor management, collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, and distribution.

B2.9.2 There shall be a written procedure for the management of external audits and inspections.

B2.9.2.1 Documentation of results of inspection and accreditation visits shall be maintained indefinitely.

B2.9.3 Quality audits shall be conducted by an individual with sufficient expertise to identify problems, but who is not directly responsible for the process being audited.

B2.9.4 Collection and analysis of data related to the audit shall be reviewed, reported, and documented, at a minimum, on an annual basis.

B2.9.5 The results of audits shall be used to recognize problems, detect trends, and identify improvement opportunities.

B2.9.6 Audit results shall be shared with the appropriate Director and/or Medical Director, supervisor of the area audited, and other relevant staff.

B2.10 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures to address errors, accidents, biological product deviations, adverse events, variances, and complaints, including the following activities at a minimum:

B2.10.1 Detection.

B2.10.2 Investigation.

B2.10.2.1 A thorough investigation shall be conducted by the CBB in collaboration with the CB Collection Site, CB Processing Facility, registry, and/or Clinical Program, as appropriate.

B2.10.3 Documentation.

B2.10.3.1 Cumulative files of errors, accidents, biological product deviations, adverse events, variances, and complaints shall be maintained.

B2.10.3.2 A written report of the investigation including conclusions, follow-up, and corrective action, if applicable, shall be prepared and maintained as part of the record for that final CB unit and maintained in the applicable cumulative file.

B2.10.3.3 Investigation reports shall be reviewed and signed by the CBB Director or designee.

B2.10.3.4 Records of all severe or unexpected adverse events or adverse reactions during CB collection and infusion shall be maintained.

B2.10.4 Tracking.

B2.10.4.1 Errors, accidents, biological product deviations, adverse events, variances, and complaints shall be tracked and trended in order to categorize and identify system problems and initiate corrective action.

B2.10.4.2 Investigation reports shall be utilized in quality monitoring and tracking in order to analyze trends.

B2.10.5 Evaluation.

B2.10.5.1 Planned variances shall be pre-approved by the appropriate CBB Director and/or Medical Director, representatives from the QM Program, and other staff as appropriate.

B2.10.5.2 Unplanned variances and associated corrective action, if necessary, shall be reviewed by the appropriate CBB Director and/or Medical Director, representatives from the QM Program, and other staff as appropriate.

B2.10.5.3 The CBB Director or designee shall review all errors, accidents, biological product deviations, adverse events, variances, and complaints. This review shall be documented.

B2.10.5.4 Each complaint shall be evaluated to determine if the complaint is related to a product deviation or adverse reaction. Corrective action shall be initiated when appropriate.

B2.10.6 Reporting.

B2.10.6.1 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.

B2.10.6.2 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.

B2.10.7 Corrective action.

B2.10.7.1 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.

B2.10.7.2 Corrective actions shall include the initiation of retraining and/or re-education of employees and performing follow-up audits of deficiencies, as appropriate.

B2.10.7.3 Documentation of the corrective action shall include the nature of the problem requiring corrective action and the identity and disposition of the affected CB unit, if indicated.

B2.10.7.4 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.

B2.10.7.5 Corrective actions shall be evaluated by the appropriate Director and/or Medical Director, or designee, representatives from the QM Program, and other appropriate staff.

B2.11 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for qualification of vendors, equipment, supplies, and reagents.

B2.11.1 Qualification studies shall be reviewed and approved by the CBB Director or designee from the QM Program.

B2.12 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for validation of significant procedures of the CBB functions.

B2.12.1 Determination of which critical procedures to be validated shall be made by the CBB Director or CBB Medical Director in collaboration with representatives of the QM Program.

B2.12.2 Validation studies shall be reviewed and approved by the CBB Director or designee from the QM Program.

B2.12.3 Records shall be maintained to document that procedures have been validated to achieve the expected end-points, including viability of CB cells and product characteristics.

B2.13 The QM Plan shall include, or summarize and reference, processes for CB unit tracking, tracing, and linkage that allow tracking and tracing of the CB unit from the infant donor to the recipient or final disposition.

B2.13.1 Linkage of the CB unit to the infant donor and mother shall be retained confidentially and indefinitely.

B2.13.2 Documentation of all facilities involved in each stage of CB unit manufacturing shall be established and maintained.

B2.14 The QM Plan shall include, or summarize and reference, processes to track and evaluate details of clinical outcome data.

B3 FACILITIES AND SAFETY

B3.1 All CBB facilities and sites shall be safe, sanitary, and secure.

B3.1.1 The CBB space shall be of adequate size, construction, and location to maintain safe operations, prevent contamination, and ensure orderly handling.

B3.1.2 The CBB space shall be maintained in a clean, sanitary, and orderly manner to prevent introduction, transmission, or spread of communicable disease.

B3.1.3 Separate areas shall be maintained for processing and storage of CB units to prevent mix-ups, product contamination, and cross-contamination.

B3.1.4 The CBB shall be secure to prevent the admittance of unauthorized individuals.

B3.2 There shall be policies and Standard Operating Procedures for biological, chemical, and radiation safety as appropriate, including:

B3.2.1 Communicable disease agents.

B3.2.2 Chemical hygiene.

B3.2.3 Hand washing.

B3.2.4 Fire safety.

B3.2.5 Radiation safety, if applicable.

B3.2.6 Latex allergy.

B3.2.7 Power failures.

B3.2.8 Liquid nitrogen.

B3.2.9 Discard of medical waste.

B4 CORD BLOOD BANK OPERATIONS

B4.1 The responsibilities of each CB Collection Site, CB Processing Facility, collecting licensed health care professional, and registry as they relate to the CBB shall be clearly defined and documented.

B4.1.1 A CBB that includes multiple CB Collection Sites and/or CB Processing Facilities shall employ coordinated policies and Standard Operating Procedures, protocols, staff training and competency evaluation procedures, and quality assessment systems.

B4.1.2 A CBB that includes multiple CB Collection Sites and/or CB Processing Facilities shall demonstrate evidence of regular interaction between these CB Collection Sites and/or CB Processing Facilities and the CBB.

B4.2 The CBB shall be responsible for all components of CB unit manufacturing, including at a minimum:

B4.2.1 Donor recruitment and consent processes.

B4.2.2 Infant donor and maternal screening and testing.

B4.2.3 Donor eligibility determination.

B4.2.4 Documentation of infant donor health at birth.

B4.2.5 Collection.

B4.2.6 Testing.

B4.2.7 Processing.

B4.2.8 Labeling.

B4.2.9 Cryopreservation.

B4.2.10 Storage.

B4.2.11 Release for listing.

B4.2.12 Listing CB units available for search.

B4.2.13 Selection and reservation.

B4.2.14 Release of the CB unit for administration.

B4.2.15 Transportation and shipping.

B4.2.16 CB unit records.

B4.2.17 CB unit disposition.

B4.3 The CBB shall have written policies and procedures addressing recipient follow-up and outcome analysis.

B4.4 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, distribution, and/or disposal.

B4.4.1 Records shall identify the person immediately responsible for each step and include appropriate dates and times to provide a complete history of the work performed and to relate the records to a particular CB unit.

B4.4.2 Records shall be as detailed as necessary for a clear understanding by a person experienced in CBB procedures.

B4.5 The CBB shall have an established relationship with each fixed CB Collection Site to ensure implementation of and compliance with the CBB QM Program and Standard Operating Procedures.

B4.6 For collection of CB units at non-fixed CB Collection Sites, the CBB shall have a written agreement with and informed consent from the infant donor family and shall have communicated with the collecting licensed health care professional.

B4.6.1 The CBB shall provide the appropriate policies, Standard Operating Procedures, and materials for the collection, labeling, storage, packing, and transport or shipment of the CB unit, reference samples, and maternal samples.

B4.6.2 The CBB shall monitor the quality of the CB unit collections through its QM Program.

B4.7 The CBB shall utilize an HLA testing laboratory accredited by the American Society for Histocompatibility and Immunogenetics (ASHI), the European Federation for Immunogenetics (EFI), or equivalent accrediting organization outside North America and Europe.

B4.8 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.

B4.8.1 The CBB shall maintain documentation of the accreditation, certification, or licensure of these laboratories to perform this testing.

B4.8.2 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.

B4.9 Confidentiality.

B4.9.1 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.

B4.9.2 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.

B4.9.3 Employee records shall be maintained in a confidential manner as required by Applicable Law.

B4.10 Quality control procedures shall be developed to monitor the continuing adequacy of the procedures, reagents, equipment, and supplies as used under routine operating conditions by the CBB personnel.

B4.10.1 The results of ongoing internal monitoring shall be documented and checked, and trends shall be analyzed on a regular basis.

B4.11 There shall be a process for the regular review of records and for the assessment of record review to identify recurring problems, potential points of failure, or need for process improvement.

B4.12 The CBB shall maintain sufficient critical outcome data to ensure that the procedures in use in the CBB consistently provide a safe and effective product.

B4.13 Institutional Review Board or Ethics Committee Requirements.

B4.13.1 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 Office of Human Research Protections under the United States Department of Health and Human Services (HHS), the United States Food and Drug Administration (FDA), or non-U.S. equivalent.

B4.13.2 The CBB shall maintain documentation of all its research protocols, Institutional Review Board or Ethics Committee approvals or equivalent, investigational new drug or device exemptions, annual reports, and any adverse events.

B5 LABELING

B5.1 Labeling operations shall be conducted in a manner adequate to prevent mislabeling or misidentification of CB units, reference samples, maternal samples, and associated documents, including the following controls at a minimum:

B5.1.1 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 ensure accuracy regarding identity, content, and conformity.

B5.1.1.1 Print-on-demand label systems shall be validated to ensure accuracy regarding identity, content, and conformity of labels to templates approved by the CBB Director or designee.

B5.1.2 A system for label version control shall be employed.

B5.1.3 There shall be processes to verify that all labels in use are accurate, legible, and maintain physical integrity.

B5.1.3.1 A system of checks in labeling procedures shall be used to prevent errors in transferring information to labels.

B5.1.3.2 All labeling shall be clear, legible, and printed using indelible ink.

B5.1.3.3 The label shall be validated as reliable for storage under the conditions in use.

B5.1.4 All data fields on labels shall be completed.

B5.1.5 When the label has been affixed to the CB unit bag, a sufficient area of the bag shall remain uncovered to permit inspection of the contents.

B5.1.6 CB units that are subsequently re-packaged into new containers shall be labeled with new labels before they are detached from the original container.

B5.1.6.1 The information entered manually on the CB unit bag label shall be verified by at least two (2) staff members prior to allowing the CB unit to progress to the next stage of processing, storage, or distribution.

B5.1.6.2 The process to establish linkage between original and new labels shall be validated.

B5.1.6.3 This linkage shall be maintained as a permanent part of the CB unit record.

B5.1.7 Stocks of unused labels representing different products shall be stored and maintained in a controlled manner to prevent errors.

B5.1.8 Unused obsolete labels shall be destroyed.

B5.1.9 Representative obsolete labels shall be archived indefinitely.

B5.2 Identification.

B5.2.1 There shall be a human and machine-readable system of identification for the CB unit, reference samples, maternal samples, and associated documents.

B5.2.2 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.

B5.2.2.1 There shall be processes to ensure that the CB unit identifier is unique to prevent errors in identification.

B5.2.2.2 If a single CB collection is stored in multiple portions, there shall be a system to identify each portion.

B5.2.3 Facilities may designate an additional or supplementary numeric or alphanumeric identifier to the CB unit, reference sample, or maternal sample.

B5.2.3.1 Supplementary identifiers shall not obscure the original identifier.

B5.2.3.2 No more than one supplementary identifier shall be visible on a CB unit bag.

B5.2.3.3 The facility associated with each identifier shall be documented.

B5.3 The information provided on the label by the CB Collection Site shall be maintained indefinitely as part of the CB unit record.

B5.4 Label Content.

B5.4.1 There shall be processes to ensure the content of each label is compliant with Applicable Law and the requirements of these Standards.

B5.4.2 Each label shall include at least the required information detailed in Appendix I, Cord Blood Unit Labeling Table.

B5.4.3 A CB unit bag with a partial label shall be accompanied by the required information detailed in Appendix I, Cord Blood Unit Labeling Table attached securely to the CB unit on a tie tag or enclosed in a sealed package to accompany the CB unit.

B5.4.4 A partial label at a minimum shall be present on the CB unit during all stages of processing.

B5.5 Elements detailed in Appendix III, Accompanying Documents at Distribution to a Clinical Program, shall accompany the CB unit at distribution to a Clinical Program, according to Applicable Law.

B5.6 If required by Applicable Law, the CB unit label shall include:

B5.6.1 For products under Investigational New Drug Application the statement: "Caution: New Drug—Limited by Federal (or United States) law to investigational use."

B5.6.2 For licensed products, the statement "Rx Only."

B6 EQUIPMENT

B6.1 All critical equipment shall be defined, qualified, and validated for the intended use.

B6.2 Equipment used 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.

B6.3 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.

B6.3.1 Equipment records shall be maintained for a minimum of 10 years after distribution of the CB unit.

B6.4 Calibration.

B6.4.1 Equipment shall be observed, tested, and calibrated on a regularly scheduled basis as recommended by the manufacturer, after a repair or move, or, at a minimum, annually.

B6.4.2 Calibration acceptance criteria shall be defined.

B6.4.3 Records of the dates and copies of calibration results shall be maintained.

B6.5 Maintenance and repairs.

B6.5.1 Equipment shall be maintained in a clean and orderly manner and located so as to facilitate cleaning and maintenance according to established schedules.

B6.5.2 Records of the maintenance schedule; maintenance performed; and damage, malfunction, modification, or repair to equipment shall be maintained.

B6.6 Cleaning and sanitation.

B6.6.1 Equipment shall be cleaned and sanitized according to established schedules.

B6.6.2 Records of equipment cleaning and sanitation shall be maintained.

B6.7 Equipment shall be routinely inspected for cleanliness, sanitation, and calibration and to ensure adherence to applicable equipment maintenance schedules.

B6.8 Records of recent maintenance, cleaning, sanitizing, calibration, and other activities shall be displayed on or near each piece of equipment.

B7 SUPPLIES AND REAGENTS

B7.1 Critical reagents and supplies shall be defined and qualified to function as expected.

B7.2 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.

B7.3 Vendors for all critical reagents and supplies shall be qualified.

B7.4 Supplies and reagents that come into contact with the CB unit shall be sterile.

B7.4.1 Sterilization of supplies and reagents prepared within the facility shall be documented.

B7.5 Supplies and reagents should be used in a manner consistent with instructions provided by the manufacturer.

B7.6 Supplies and reagents used for CB collection, processing, or cryopreservation, whenever possible, shall be approved for human use.

B7.6.1 Supplies and reagents shall be of the appropriate grade for the intended use.

B7.7 Certificates of analysis shall be obtained and maintained indefinitely on file for all critical reagents.

B7.8 Receipt, inspection, verification, acceptance, and storage of supplies and reagents shall be documented.

B7.8.1 The disposition of rejected supplies and reagents shall be documented.

B7.9 The lot number, expiration date, and manufacturer of supplies and reagents used for the collection and processing of each CB unit shall be documented.

B8 INVENTORY MANAGEMENT

B8.1 The inventory management system shall clearly distinguish directed CB units from unrelated CB units.

B8.2 The inventory management system for CB units shall ensure each CB unit and its associated reference samples, maternal samples, and records can be located in a timely way. The inventory records shall include:

B8.2.1 CB unit unique identifier.

B8.2.2 Maternal donor identifier.

B8.2.3 Storage device identifier.

B8.2.4 Location within the storage device.

B8.3 The inventory management system shall be designed to prevent mix-ups, contamination of the CB units during storage, and the improper release of quarantined CB units.

B8.4 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.

B8.5 The CBB shall have policies related to the return of CB units to the CBB inventory.

B8.5.1 Unrelated allogeneic CB units shall not be returned to the CBB inventory after they have left the CBB premises.

B8.5.2 If directed allogeneic or autologous CB units are returned to the CBB inventory, there shall be documentation of appropriate storage and transportation.

B9 INVENTORY TRANSFER

B9.1 If all or part of a CB unit inventory is to be transferred to another CBB:

B9.1.1 The CBB shall have policies and Standard Operating Procedures describing the transfer of inventory.

B9.1.2 There shall be a written agreement between the transferring and accepting CBBs that describes the responsibilities of each CBB, including the elements in B9, at a minimum.

B9.1.3 There should be a mechanism to contact the transferring CBB Director or designee for future reference, as defined in the contract or agreement.

B9.2 Inventory transferred to another CBB shall be accompanied by the following at a minimum:

B9.2.1 All collection and processing records, including medical and genetic history, identity and results of all maternal and CB unit testing, summary records of donor eligibility determination, and cryopreservation records, including freezing curve.

B9.2.2 All associated reference samples and maternal samples.

B9.2.3 The complete storage history of each CB unit, including the storage temperature records and records of any transfer of a CB unit to a different storage location.

B9.3 The transferring and accepting CBBs shall collaborate to ensure that:

B9.3.1 The inventory is transferred in a manner that maintains proper storage temperature and prevents mix-ups and contamination.

B9.3.2 Transport and shipping does not adversely affect the integrity of the CB units.

B9.3.3 The safety of transporting and shipping personnel is ensured.

B9.4 There shall be policies to maintain confidentiality.

B9.5 Responsibilities of the accepting CBB.

B9.5.1 Records shall be in a language and form that can be understood by the accepting CBB personnel.

B9.5.2 There shall be documentation of review of records and transferred inventory to ensure that:

B9.5.2.1 The CB units were stored in appropriate storage bags at appropriate storage temperatures.

B9.5.2.2 Maintenance of appropriate storage conditions throughout the period of storage can be documented.

B9.5.2.3 Integrally attached segments and other reference samples and maternal samples for each CB unit are included in the transferred inventory.

B9.5.2.4 Records are available to link each CB unit to its infant donor; its reference samples and maternal samples; and all relevant history, collection, processing, cryopreservation, and testing records.

B9.5.3 Records received shall include at a minimum:

B9.5.3.1 Maternal consent.

B9.5.3.2 Medical and genetic history.

B9.5.3.3 Identity and results of all maternal and CB unit communicable disease tests.

B9.5.3.4 CB unit cell counts and sterility testing.

B9.5.3.5 Processing methods.

B9.5.3.6 Cryopreservation records, including freezing curve.

B9.5.3.7 The manufacturer and approximate dimensions of the storage bag and canister.

B9.5.3.8 Enumeration of attached segments and other reference samples.

B9.5.4 There shall be access to all records described in B10.

B9.5.5 There shall be a process for inspecting incoming CB units for damage and contamination.

B9.5.6 After the CB units have been transferred, but before the transferred inventory is made available for search:

B9.5.6.1 The integrity and viability of thawed CB units shall be verified to ensure the transport or shipping method did not compromise CB unit viability.

B9.5.6.2 There shall be confirmation of the completeness of the records including donor identity and HLA typing results.

B9.5.6.3 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.

B10 DOCUMENTS AND RECORDS REQUIREMENTS

B10.1 A record management system shall be established and maintained to ensure protection, preservation, integrity, and ready retrieval of records.

B10.1.1 Records shall be available for inspection by authorized individuals upon request from a regulatory or accrediting agency.

B10.2 If records are maintained in more than one location and/or format, there shall be a system to ensure prompt identification, location, and retrieval of all records.

B10.3 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.

B10.3.1 Records of CB units manufactured in or exported to the U.S. shall be in English or, if in another language, shall be translated to English and accompanied by a statement of authenticity by the translator prior to release of the CB unit.

B10.4 The following CBB records shall be maintained indefinitely:

B10.4.1 Infant donor and parental records.

B10.4.2 CB unit records related to collection, processing, storage, and distribution.

B10.4.3 QM records.

B10.4.4 Personnel records.

B10.5 Records in case of divided responsibility.

B10.5.1 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.

B10.5.2 The CBB shall maintain a listing of the names, addresses, and responsibilities of other facilities that perform manufacturing steps on a CB unit.

B10.5.3 There shall be a system to allow the CBB access to information that tracks all manufacturing steps performed by other facilities.

B10.5.4 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.

B10.6 Electronic Records Requirements.

B10.6.1 If an electronic record-keeping system is used, there shall be a system to ensure the authenticity, integrity, and confidentiality of all records throughout the period of record retention.

B10.6.2 A system shall be established for review of data before final acceptance.

B10.6.3 There shall be the ability to generate true copies of the records in both paper and electronic format suitable for inspection and review.

B10.6.4 There shall be a back-up or alternative system for all electronic records that ensures continuous operation in the event that primary electronic data are not available.

B10.6.4.1 Documentation of periodic testing of the alternative system shall be maintained.

B10.6.5 There shall be a system that limits access to the electronic records to only authorized individuals.

B10.6.6 All system modifications shall be authorized, documented, and validated prior to implementation.

B10.6.7 The electronic record system shall ensure that all infant donor, CB unit, and patient identifiers are unique.

B10.6.8 When an electronic system is used, there shall be validated procedures for:

B10.6.8.1 Systems development.

B10.6.8.2 Numerical designation of system versions, if applicable.

B10.6.8.3 Prospective validation of the system(s), including hardware, software, and databases.

B10.6.8.4 Installation of the system(s).

B10.6.8.5 Training and continuing competency of personnel in use of the system(s).

B10.6.8.6 Monitoring of data integrity.

B10.6.8.7 Backup of the electronic record system(s) on a regular schedule.

B10.6.8.8 System maintenance and operations.

B10.6.8.9 Electronic record entry, verification, and revision including review of data before final acceptance.

B11 INTERRUPTION OF OPERATIONS AT ESTABLISHED SITES

B11.1 In the event that any CB collection or processing function is discontinued for a period exceeding six months, there shall be documentation of the training and continued competency of all staff to perform the duties assigned upon resumption of activities.

B11.2 If CB collection activity is discontinued at any fixed CB Collection Site for a period exceeding six months, the CBB Director or designee shall review and renew the CB collection contract with that site.

B11.3 If a CBB discontinues processing of new CB units:

B11.3.1 There shall be competent staff to oversee, maintain, and distribute the inventory.

B11.3.1.1 The staff shall maintain communication with all relevant registries and Clinical Programs, if applicable.

B11.3.2 A process to distribute CB unit contiguous segments and samples for testing shall be maintained.

B11.3.3 All records of the entire inventory in storage shall be maintained.

B11.4 Prior to the reestablishment of either CB collection or processing, as applicable, the following at a minimum shall be documented:

B11.4.1 Review of all procedures to ensure that methods are consistent with current practices.

B11.4.2 Inspection of all reagents and supplies to ensure none will be used past its expiration date.

B11.4.3 Validation, calibration, and maintenance of all equipment have been completed within the time periods specified in the Standard Operating Procedures and manufacturer's instructions.

B11.5 Cessation of operations.

B11.5.1 The CBB shall follow all contractual obligations that are made with the directed infant donor families.

PART C: CORD BLOOD DONOR MANAGEMENT AND COLLECTION STANDARDS

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 Procedures
C7	Transportation and Shipping of Non-Cryopreserved 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 The CB Collection Site shall have processes to prevent the introduction, transmission, or spread of communicable disease.

C1.2 Fixed CB Collection Site.

C1.2.1 There shall be a written agreement describing the interaction between the fixed CB Collection Site and the CBB.

C1.2.2 There shall be adequate space for the performance of the collection procedure.

C1.2.3 There shall be adequate space for secure storage of the CB unit, associated reference samples and maternal samples, and documents until they are transported or shipped to the CB Processing Facility.

C1.2.4 There shall be a designated area for appropriate and secure storage and preparation of the reagents, supplies, and equipment needed for the collection procedures.

C1.2.4.1 Reagents and supplies shall be stored according to the manufacturer's recommendations and used prior to the expiration dates.

C1.2.5 Records supplied to the CBB shall include the following at a minimum:

C1.2.5.1 Identity of supplies and reagents including manufacturer, lot number, and expiration date.

C1.2.5.2 Documentation of appropriate storage of all supplies, reagents, CB units, reference samples, and maternal samples.

C1.3 Non-Fixed CB Collection Site.

C1.3.1 For directed donations, there shall be a written agreement between the infant donor family and the CBB related to CB unit collection and transport or shipping.

C1.3.2 For unrelated donations, there shall be a written agreement between the licensed health care professional and the CBB regarding the CB unit collection and transport or shipping.

C1.3.3 The CBB Medical Director or designee shall be responsible for ensuring that there are policies and Standard Operating Procedures applicable to the non-fixed CB Collection Site that meet the requirements of these Standards and address at least collector training, storage, security of the supplies and reagents, completion of documents, the collection procedure, labeling, storage, and transportation or shipment.

C1.3.4 Reagents, supplies, and equipment needed for the collection procedure shall be stored in an area and manner appropriate to protect their integrity and functionality.

C1.3.5 When a CB collection kit is prepared and sent from the CBB, there shall be adequate instructions and materials provided to collect, label, store, pack, and transport or ship the CB unit.

C1.3.5.1 The stability of temperature of the kit during transportation or shipment shall be validated or monitored from the time it leaves the CBB to the return of the kit to the CBB.

C1.3.5.2 Documentation of these parameters shall be provided to the CBB and maintained in the CB unit file.

C1.3.6 Temporary storage of the CB unit, reference samples, maternal samples, and documents shall be secure until they are transported or shipped to the CB Processing Facility.

C2 CORD BLOOD COLLECTION PERSONNEL REQUIREMENTS

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

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

C2.2.1 At non-fixed CB Collection Sites, the CBB shall provide a mechanism for the collecting licensed health care professional to communicate with the CBB Medical Director or designee for any problems with the collection.

C2.3 Where there are CB Collection Sites that are not staffed by the CBB personnel, there shall be a designated individual who is responsible for the daily operation of the CB Collection Site and communication with the CBB Medical Director or designee.

C2.3.1 Personnel not employed by the CBB shall comply with these Standards.

C2.3.2 At CB Collection Sites where individual licensed health care professionals perform collections, the individual licensed health care professional may be the contact person.

C2.4 All collections shall be performed by personnel trained for the collection procedure.

C2.5 At non-fixed CB Collection Sites:

C2.5.1 There shall be documentation that a licensed health care professional has agreed to perform the collection.

C2.5.2 Training shall cover each aspect of the CB collection process, including at least the use of the CB collection kit provided, cleaning of the cord, use of the CB collection bag to avoid microbial contamination and clots, labeling, identity check, and storage.

C2.5.3 Training shall be documented.

C3 POLICIES AND STANDARD OPERATING PROCEDURES

C3.1 The CB Collection Site shall have clearly written policies and Standard Operating Procedures that are precise and unambiguous and that address all aspects of the collection operation, meet the requirements of these Standards, and are consistent with the Standard Operating Procedures of the CBB.

C3.2 All collection personnel shall follow the policies and Standard Operating Procedures established by the CBB for the CB Collection Site.

C3.2.1 Current copies of the policies and Standard Operating Procedures relevant to the processes being performed shall be available to the CB Collection Site personnel at all times.

C3.2.2 The appropriate staff shall be trained and competency established on new and revised policies and Standard Operating Procedures prior to performing the task. This review, associated training, and competency shall be documented.

C3.3 There shall be policies and Standard Operating Procedures to cover at least the following:

C3.3.1 Donor recruitment.

C3.3.2 Maternal screening (including interpretation and acceptable results).

C3.3.3 Informed consent.

C3.3.4 Donor eligibility criteria and determination.

C3.3.5 Documentation of infant donor health at birth.

C3.3.6 Infant donor screening (including interpretation and acceptable results).

C3.3.7 Maintenance of linkage of the CB unit to the infant donor and mother.

C3.3.8 Collection of CB, reference samples, and maternal samples.

C3.3.9 Labeling of the CB unit, reference samples, maternal samples, and associated documents.

C3.3.10 Storage of CB units, reference samples, maternal samples, and documentation.

C3.3.11 Transport and shipping of the CB unit, reference samples, maternal samples, and documentation to the CB Processing Facility.

C3.3.12 Personnel training and documentation of continued competency for the procedures performed.

C3.3.13 Facility management including supplies, maintenance and monitoring of equipment, cleaning and sanitation procedures, disposal of medical and biohazardous waste, emergency and safety procedures, and a disaster plan.

C4 INFORMED CONSENT

C4.1 Informed consent shall be obtained and documented from the mother.

C4.1.1 In cases of a surrogate mother, informed consent shall be obtained and documented from both the surrogate mother and the genetic mother.

C4.1.2 Informed consent shall be obtained and documented while the mother is able to concentrate on the information and is not distracted by aspects of labor.

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 mother shall have an opportunity to ask questions.

C4.4 Consent for at least the collection procedure shall be obtained and documented prior to delivery, including the following information at a minimum:

C4.4.1 An explanation of the collection procedure in terms the mother can understand.

C4.4.2 The possible risks and benefits of CB collection.

C4.4.3 The right of the mother to refuse the collection without prejudice at any time.

C4.4.4 The mother will be approached at a later time for complete consent, including consent to process, bank, and release the CB unit for administration and all of the elements in Section C4.5.

C4.4.5 Any services that will be performed prior to obtaining full consent to process, bank, and release the CB unit for administration.

C4.5 Prior to processing, full consent shall be obtained and documented, including the following information at a minimum:

C4.5.1 The overall purpose and participation of the mother and infant donor.

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 mother and/or infant donor.

C4.5.4 The possible alternatives to participation.

C4.5.5 The right of the mother to refuse without prejudice.

C4.5.6 The intent of the donation for either unrelated use or for directed allogeneic or autologous use.

C4.5.6.1 If the CB unit is intended for unrelated allogeneic use, the mother shall be informed that the CB unit is a donation that will be made available to other individuals and will not necessarily be available to the infant donor or the infant donor's family at a later date.

C4.5.6.2 If the CB unit is intended for directed allogeneic or autologous use, the mother shall be informed that the release of the CB unit will be limited respectively to the family, intended recipient(s), or the infant donor.

C4.5.6.3 If the CB unit may potentially be used for reasons other than the primary intent, this shall be fully disclosed in the informed consent.

C4.5.7 The mother will be asked to provide personal and family medical history.

C4.5.8 Personnel will be permitted to review the medical records of the mother and infant donor.

C4.5.9 Reference samples and maternal samples will be collected.

C4.5.9.1 A sample will be collected from the mother for communicable disease testing and other testing, as applicable.

C4.5.9.2 Reference samples and maternal samples will be collected for communicable disease testing, genetic disease testing, HLA typing, and other testing, as applicable.

C4.5.10 Reference samples and maternal samples will be stored for future testing.

C4.5.11 The CBB will maintain linkage for the purpose of notifying the infant donor's mother or family and/or her physician of communicable or genetic diseases, whenever possible.

C4.5.11.1 The CBB retains the right to follow up with the mother or her primary physician at a future date.

C4.5.11.2 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 by national authorities to evaluate the CBB.

C4.5.11.3 Linkage between the infant donor and mother with the CB unit shall be maintained indefinitely.

C4.5.12 Possible uses of the CB unit for purposes other than clinical transplantation.

C4.5.13 The CBB's policies for disposal of CB units, including at a minimum:

C4.5.13.1 Nonconforming CB units.

C4.5.13.2 Directed allogeneic or autologous CB units, if no longer required.

C5 MATERNAL AND INFANT DONOR EVALUATION

C5.1 There shall be criteria and evaluation procedures in place to protect the safety and confidentiality of the infant donor and mother.

C5.1.1 Maternal and infant donor eligibility shall be determined based upon results of screening and testing in accordance with Applicable Law.

C5.1.2 Infant donor and maternal evaluation results shall be documented.

C5.1.3 There shall be a policy for follow-up of donors and the management of donation-associated adverse events.

C5.2 There shall be infant donor and mother evaluation procedures in place to evaluate the risk of disease transmission from CB units.

C5.2.1 If a directed CB unit may potentially be used for unrelated donation, the evaluation process shall include all evaluation requirements for unrelated allogeneic CB units at the time of donation.

C5.3 Maternal Screening.

C5.3.1 There shall be written criteria for maternal screening.

C5.3.2 A medical and genetic history of the infant donor's family (parents, grandparents, siblings, and parents' siblings including egg, sperm, or embryo donor, if applicable) shall be obtained and documented.

C5.3.2.1 The history shall be obtained and documented while the mother is able to concentrate on the information and is not distracted by aspects of labor.

C5.3.2.2 The history shall collect information to include at a minimum genetic history, malignant disease, and inherited disorders that are transmissible to the recipient in the mother's and father's family including infant donor's grandparents, if appropriate.

C5.3.2.3 The CBB shall have policies to defer a donor or collected CB unit from unrelated allogeneic use if there is a family history of a genetic or malignant disease, according to Applicable Law, that could transmit to a recipient unless testing or follow-up excludes the risks.

C5.3.3 A history for the mother's communicable disease risk behavior shall be obtained and documented.

C5.3.3.1 The mother's communicable disease risk behavior shall be obtained in a confidential manner.

C5.3.3.2 The history shall include the mother's prenatal communicable disease testing, if known, and results of other general medical testing that could influence communicable disease transmission.

C5.3.3.3 Previously obtained history for communicable disease transmission risk shall be updated to the time of delivery. This shall be completed within 14 days after delivery.

C5.3.3.4 In the case of a surrogate mother who carries an infant donor not genetically hers to delivery, a communicable disease risk history of the surrogate mother shall be obtained and documented.

C5.3.3.5 The communicable disease risk history of the sperm, egg, or embryo donor shall be obtained and documented, if applicable.

C5.3.3.6 The mother's and surrogate mother's, if applicable, travel history shall be obtained and documented. Travel-related donor eligibility shall be determined according to Applicable Law and documented.

C5.3.3.7 Screening for human transmissible spongiform encephalopathy, including Creutzfeldt-Jakob disease, shall be documented.

C5.3.3.8 The mother and surrogate mother, if applicable, shall confirm that all the information provided is true to the best of her knowledge.

C5.3.3.9 The CBB shall have policies regarding the acceptance of nonconforming CB units for unrelated allogeneic use if there is a communicable disease risk that may adversely affect the recipient.

C5.3.4 When a mother does not meet the established screening criteria, the CBB Medical Director or CB Collection Site Director shall document and maintain in the permanent record the nature of the variances and the rationale for inclusion of that CB unit.

C5.4 Maternal Samples.

C5.4.1 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 D11.1.

C5.4.2 A sufficient volume of blood from the birth mother shall be obtained to meet D5.2.1.

C5.4.3 A sufficient volume of blood from the genetic mother including egg donors, if possible, shall be obtained to meet D5.2.2.

C5.5 Infant Donor Screening and Testing.

C5.5.1 History of the current pregnancy and delivery and the infant donor's birth data shall be obtained and documented, including gender, gestational age, other results of clinical examination, and any finding suggestive of disease potentially transmissible through administration of a CB unit.

C5.6 The mother shall be provided with information to contact the CBB if the infant donor later develops a serious disease.

C6 CORD BLOOD COLLECTION PROCEDURES

C6.1 CB collection procedures and practices shall protect the mother and the 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 ensure the safety of the mother and the infant donor.

C6.2.1 CB collections should only be performed *in utero* 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 shall only occur in uncomplicated deliveries as determined by the licensed health care professional responsible for the delivery.

C6.2.3 Unrelated CB units collected *in utero* shall only be obtained from infant donors after a minimum of 34 weeks' gestation.

C6.2.4 Directed allogeneic and autologous 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 mother shall be verified.

C6.3.2 The identity of the collecting licensed health care professional 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.

C6.3.5 The primary CB collection bag shall be approved for use with human blood and shall be used and sealed to prevent leakage and minimize the risk of cell loss and of microbial contamination.

C6.3.6 All reagents and supplies for CB collection that come into contact with the CB unit shall be sterile.

C6.4 There shall be a unique numeric or alphanumeric identifier for the CB unit, reference 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, reference samples, maternal samples, and associated documents that permits tracking and tracing among the CB unit, infant donor, infant donor's mother, reference samples, maternal samples, and documentation.

C6.6 At completion of CB collection, the primary collection bag shall bear or be accompanied by the information required in Appendix I, Cord Blood Unit Labeling Table.

C6.7 There shall be a written policy for storage of CB units, reference 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, reference samples, and maternal samples shall be maintained in a secure environment.

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

C6.8 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 NON-CRYOPRESERVED 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.

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.

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 CB units shall be placed in an outer container that maintains a designated temperature range to protect cell viability during CB unit transportation and shipping as documented by prior validation of the container, a continuous recording of the temperature of the container during transportation or shipping, or another method to document maintenance of temperature within the accepted range.

C7.4.1 The outer container shall be labeled with the information required in Appendix I, Cord Blood Unit Labeling Table.

C7.4.2 The outer container shall be made of material adequate to withstand leakage of contents, shocks, pressure changes, and other conditions incident to ordinary handling during transportation or shipping.

C7.5 Transportation and Shipping Records.

C7.5.1 Transportation and shipping records shall permit the tracking of the CB unit from the CB Collection Site to its final destination.

C7.5.2 A list identifying each CB unit and its associated reference samples, maternal samples, and documents that are enclosed in a package shall be included.

C7.5.3 Transportation and shipping records shall identify:

C7.5.3.1 The CB Collection Site responsible for transporting or shipping the CB unit.

C7.5.3.2 The date and time of transport or shipment.

C7.5.3.3 The identity of the courier.

C7.5.3.4 The date and time of receipt of the package.

PART D: CORD BLOOD PROCESSING STANDARDS

PART D: CORD BLOOD PROCESSING STANDARDS

D1 CORD BLOOD PROCESSING FACILITY REQUIREMENTS

D1.1 The CB Processing Facility shall be registered and/or accredited with the appropriate governmental authority for the activities performed.

D1.2 There shall be designated facilities with adequate space for the following:

D1.2.1 Performance of processing activities and ancillary functions.

D1.2.2 Preparation of, and safe, sanitary, and orderly storage of, the supplies, reagents, and equipment needed for processing, testing, cryopreservation, storage, and release.

D1.2.3 Maintenance of records.

D1.3 The CB Processing Facility shall be secure in order to prevent the entrance of unauthorized personnel and protect daily operations, equipment, and records.

D1.4 The CB Processing Facility shall provide adequate lighting, ventilation, plumbing, drainage, and access to sinks and toilets to prevent the introduction, transmission, or spread of communicable disease in compliance with Applicable Law.

D1.5 There shall be documentation of facility cleaning and sanitation, environmental conditions, and inspection of environmental control systems to ensure adequate conditions for proper operations in compliance with Applicable Law.

D1.6 Environmental conditions for temperature, humidity, ventilation, and air filtration and classification shall be defined and, if appropriate, monitored.

D1.7 Facility Safety Requirements.

D1.7.1 The CB Processing Facility shall have programs operating in compliance with Applicable Law that are designed to minimize risks to the health and safety of employees, volunteers, and visitors.

D1.7.2 There shall be procedures for biological, chemical, and radiation safety as appropriate, including:

D1.7.2.1 Bloodborne pathogens.

D1.7.2.2 Chemical hygiene.

D1.7.2.3 Hand washing.

D1.7.2.4 Fire safety.

D1.7.2.5 Radiation safety, if applicable.

D1.7.2.6 Latex allergy.

D1.7.2.7 Power failures.

D1.7.2.8 Liquid nitrogen.

D1.7.3 The CB Processing Facility shall have written policies and procedures for action in case of exposure to communicable disease or to chemical, biological, radiological, or liquid nitrogen hazards.

D1.7.4 Decontamination and disposal techniques for medical waste shall be described.

D1.7.4.1 Human tissue shall be disposed in a manner to minimize hazard to facility personnel and the environment.

D1.7.5 Gloves and protective clothing shall be worn while handling biological specimens. Such protective clothing shall not be worn outside the work area.

D2 CORD BLOOD PROCESSING FACILITY PERSONNEL REQUIREMENTS

D2.1 All CB Processing Facility personnel shall comply with these Standards.

D2.2 The CB Processing Facility shall have oversight of non-processing personnel visiting the CB Processing Facility to ensure compliance with these Standards.

D2.3 The CB Processing Facility shall ensure contracted processing services are in compliance with these Standards.

D3 POLICIES AND STANDARD OPERATING PROCEDURES

D3.1 The CB Processing Facility shall have clearly written policies and Standard Operating Procedures that are precise and unambiguous and address all aspects of the CB processing operation, including at a minimum:

D3.1.1 CB unit acceptance criteria, processing, cryopreservation, and storage.

D3.1.2 Labeling of the CB unit, reference samples, maternal samples, and associated documents.

D3.1.3 Storage of reference samples and maternal samples for testing.

D3.1.4 Communicable disease testing, microbial cultures, HLA typing, hemoglobinopathy testing, and other testing. Acceptance criteria for test results shall be described.

D3.1.5 Criteria for release of CB units from quarantine, including nonconforming CB units.

D3.1.6 Criteria for qualification of CB units available for search and administration, including nonconforming CB units.

D3.1.7 Personnel training and documentation of continued competency for the procedures performed.

D3.1.8 Facility management of supplies, maintenance and monitoring of equipment, cleaning and sanitation procedures, disposal of medical and biohazardous waste, and emergency and safety procedures.

D3.1.9 A disaster plan to ensure continuous safe storage and transport and shipping, if applicable, of the CB units.

D3.1.10 Discard and disposal of CB units.

D4 CORD BLOOD PROCESSING

D4.1 Acceptance Criteria.

D4.1.1 Upon receipt of a CB unit package into the CB Processing Facility, there shall be a system to verify the contents of the package against the list of enclosed items.

D4.1.2 The CB Processing Facility shall conduct an inspection of the package, including at a minimum:

D4.1.2.1 The CB unit for appropriate appearance, labeling, and identification.

D4.1.2.2 The reference samples and maternal samples for appropriate labeling, identification, and associated documents.

D4.1.2.3 The integrity of the primary and secondary containers, outer container, duration of transportation or shipment, and temperature ranges.

D4.1.3 For unrelated CB units, an appropriately signed consent authorizing processing, testing, cryopreservation, and storage of the CB unit, reference samples, and maternal samples for the intended purpose shall be present.

D4.1.4 For directed CB units, a signed agreement from the requesting family shall be present, including the name of the intended recipient if applicable, for processing, testing, cryopreservation, and storage.

D4.2 Processing.

D4.2.1 Processing of CB units shall be performed after acceptance of CB units in a properly identified container.

D4.2.2 A minimum of a partial label shall be affixed to the CB unit during all stages of processing.

D4.2.3 Information regarding processing steps that have been completed on a CB unit shall accompany the CB unit during all stages of processing.

D4.2.4 Processing and cryopreservation of CB units shall be performed according to validated Standard Operating Procedures.

D4.2.5 Cryopreservation of unrelated CB units shall be initiated within 48 hours of collection.

D4.2.6 Cryopreservation of directed CB units shall be initiated within 72 hours of CB collection.

D4.2.7 CB unit processing other than simple dilution and/or volume reduction by depletion of erythrocytes and/or plasma shall only be performed according to Applicable Law and:

D4.2.7.1 Using reagents and/or devices approved for that manipulation by the appropriate governmental agency or

D4.2.7.2 With an Institutional Review Board or Ethics Committee-approved protocol or

D4.2.7.3 With an Investigational New Drug Protocol, Investigational Device Exemption, or non-U.S. equivalent.

D4.2.8 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.

D4.2.9 Failure of the processing procedure to achieve acceptable end-points shall be evaluated and documented.

D4.3 At the completion of processing prior to cryopreservation, the freezing bag shall be labeled with or be accompanied by the information required in Appendix I, Cord Blood Unit Labeling Table.

D4.4 Records pertinent to the CB unit shall be reviewed by the CB Processing Facility Director or designee.

D5 REFERENCE SAMPLES AND MATERNAL SAMPLES

D5.1 At a minimum, the following reference samples shall be collected from the CB unit prior to cryopreservation:

D5.1.1 A minimum volume of at least 200 μL in at least two segments with each sealed and integrally attached to the freezing bag.

D5.1.1.1 The contents of each reference sample shall be representative of the CB unit.

D5.1.1.2 When a CB unit is initially requested, one (1) segment shall be used for confirmatory typing and should be used for cell viability and/or potency analysis.

D5.1.2 Additional samples of a minimum of 2 x 10^6 nucleated cells in at least two (2) vials or additional contiguous segments.

D5.1.2.1 Reference samples intended for viability or potency analysis shall be stored at -150°C or colder.

D5.1.2.2 When reference samples are stored in liquid nitrogen vapor phase at -150°C or colder, the freezers shall be qualified to show that all reference samples are maintained at appropriate temperatures.

D5.1.2.3 Reference samples used for purposes other than viability analysis shall be stored at -70°C or colder.

D5.1.3 A minimum volume of 3.6 mL of serum or plasma from non-heparinized samples in at least two vials.

D5.1.3.1 The serum or plasma should be stored at -70°C or colder.

D5.1.4 Suitable material for preparation of at least 50 μg genomic DNA.

D5.2 Maternal samples to be maintained shall include:

D5.2.1 From the birth mother, a minimum volume of 3.6 mL of serum and/or plasma from non-heparinized samples in at least two vials.

D5.2.1.1 The serum or plasma shall be stored at -70°C or colder.

D5.2.2 From the genetic mother including egg donors, if possible, suitable material for preparation of at least 50 μg genomic DNA.

D6 CRYOPRESERVATION

D6.1 CB units shall be cryopreserved using controlled rate freezing or an equivalent procedure. If an equivalent procedure is used, it shall be validated to maintain equivalent recovery and viability of nucleated cells.

D6.2 Cryopreservation Standard Operating Procedures shall specify that the following information is recorded for each unit:

D6.2.1 Total nucleated cell concentration within a defined range.

D6.2.2 The cryoprotectant, its final concentration, and the duration of cell exposure prior to freezing.

D6.2.3 Method of freezing and end-point temperature of cooling.

D6.2.4 Cooling rate within a defined range.

D6.2.5 Freezing curve parameters within a defined range.

D6.2.6 Storage temperature.

D6.3 CB units shall be stored in freezing bags designed and approved for the cryopreservation of human cells and shall be placed into metal canisters to provide protection during freezing, storage, transportation, and shipping.

D6.3.1 Each freezing bag and its satellite container(s), if any, shall be examined visually for damage or possible contamination prior to use.

D6.3.2 Freezing bags shall allow the filling of at least two contiguous segments.

D6.4 After filling, each freezing bag shall be visually examined for possible leaking, overfilling or underfilling of the freezing bag, and breakage of seals. The results of these inspections shall be documented.

D6.5 The duration from addition of cryoprotectant to initiation of freezing shall be minimized and validated by the CBB.

D6.6 The duration from completion of freezing to storage at -150ºC or colder shall be minimized and validated by the CBB.

D7 CONDITIONS FOR STORAGE

D7.1 Each CB unit storage device shall be located in a secure area. The device and/or the area shall have locking capability that is used at least when the area is not occupied by the CBB staff.

D7.2 Facilities storing CB units shall validate the duration and conditions of storage.

D7.3 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.

D7.4 Procedures to minimize the risk of microbial cross-contamination of CB units shall be defined and maintained.

D7.4.1 Each CB unit shall be maintained in quarantine storage until the CBB Director or designee has approved the release of the CB unit from quarantine status based upon review of maternal communicable disease risk history, other medical history, maternal test results, and CB unit sterility test results as required under Applicable Law.

D7.4.2 Records shall indicate when a CB unit was released from quarantine into permanent storage.

D7.4.3 CB units shall be quarantined if the reference samples or maternal samples have positive or indeterminate screening test results for communicable disease.

D7.5 Temperature.

D7.5.1 CB units shall be stored at -150^{o}C or colder.

D7.5.1.1 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.

D7.5.2 Warming events at any time after the process of storage and/or distribution shall be minimized.

D7.5.2.1 The duration of warming events shall be documented, and the impact on the CB unit shall be assessed.

D8 MONITORING AND ALARM SYSTEMS

D8.1 Refrigerators used for storage of CB units before cryopreservation of the CB unit shall have a system to monitor the temperature continuously or record the temperature every four hours at a minimum.

D8.2 Freezers used for CB unit storage where CB units are not fully immersed in liquid nitrogen shall have a system to monitor the temperature continuously or record the temperature every four hours at a minimum.

D8.3 When CB units are stored fully immersed in liquid nitrogen, the level of liquid nitrogen shall be continuously monitored or recorded every four hours at a minimum.

D8.4 Alarm Systems.

D8.4.1 Storage devices for CB units and associated reference samples and maternal samples shall have alarm systems that are continuously active.

D8.4.2 Alarm systems shall have audible and visible signals.

D8.4.3 Alarm systems shall be checked periodically for technical function. The records of such checks shall be maintained.

D8.4.4 The alarm system shall be capable of notifying designated personnel 24 hours a day.

D8.4.4.1 A procedure for notifying designated staff shall be readily accessible.

D8.4.5 Alarm parameters shall be set to allow staff sufficient time to salvage CB units, reference samples, and maternal samples.

D8.4.6 Any alarm event and its resolution shall be documented.

D8.5 Additional storage devices of appropriate temperature shall be available for CB unit storage if the primary storage device fails.

D9 DISPOSAL

D9.1 Disposal of any CB unit shall be documented.

D9.2 The records for discarded CB units shall indicate the unique numeric or alphanumeric identifier of the CB unit and the reason, date, and method of disposal; the authorizing individual; and the individual who disposed of the CB unit.

D9.3 For directed allogeneic or autologous CB unit discard:

D9.3.1 Disposal shall comply with the terms of disposal in the written agreement.

D9.3.2 Reasons for disposal shall be documented at the time of the written agreement or at the time of disposal.

D9.3.3 Documentation shall be complete before a unit is discarded.

D10 CORD BLOOD UNIT TESTING

D10.1 Testing control procedures shall include:

D10.1.1 The use of established and validated appropriate assays, standards, and test procedures for the evaluation of the CB unit.

D10.1.2 Adequate provisions for monitoring the reliability, accuracy, precision, and performance of test procedures and instruments.

D10.1.3 Adequate identification and handling of all reference samples so that they are accurately related to the specific CB unit being tested, to its infant donor, the infant donor's mother, and to the specific recipient, as applicable.

D10.2 The following tests shall be performed on a reference sample from each CB unit obtained after processing prior to cryopreservation:

D10.2.1 Total nucleated cell count.

D10.2.2 Nucleated red blood cell count.

D10.2.3 Total number of CD34 cells.

D10.2.4 Viability and/or potency as measured by viable CD34 cells and/or CFU.

D10.2.5 CBC with differential. Parameters for neutrophils, lymphocytes, monocytes, and platelets shall be defined.

D10.2.6 Microbial cultures using a system validated for the growth of aerobic and anaerobic bacteria and fungi.

D10.2.6.1 For directed CB units, the results of positive microbial tests shall include identity of the organism(s). Antimicrobial sensitivities shall be performed prior to release of the CB unit for administration. These results shall be reported to the prospective Clinical Program.

D10.2.6.2 CB units for unrelated use shall be free from microbial contamination.

D10.3 ABO group and Rh type shall be performed on a reference sample from each CB unit prior to listing.

D10.4 Human leukocyte antigen (HLA) typing shall be performed on a reference sample from each CB unit.

D10.4.1 HLA-A, B, and DRB1 loci shall be determined.

D10.4.2 HLA-C and DQB1 should be determined.

D10.4.3 HLA Class I and Class II typing shall be performed by DNA-based methods. For unrelated allogeneic CB units, this typing shall be performed before listing the CB unit for search.

D10.4.4 At a minimum, DNA high resolution molecular typing shall be performed for Class II DRB1 typing prior to release for administration.

D10.5 The following tests shall be performed on a reference sample from each CB unit prior to release for administration:

D10.5.1 Hemoglobinopathy screening.

D10.5.2 CFU from the final CB unit for unrelated allogeneic CB units.

D10.6 The CBB shall have a written policy for the management of positive or indeterminate results found during the screening process and/or laboratory testing of reference samples.

D10.7 Positive or indeterminate test results shall be communicated to the infant donor's mother or legal guardian and/or her physician according to Applicable Law.

D10.8 Prior to release to the Clinical Program, each CB unit should be tested for evidence of infection by at least the following communicable disease agents using licensed donor screening tests when available according to Applicable Law:

D10.8.1 Human immunodeficiency virus, type 1.

D10.8.2 Human immunodeficiency virus, type 2.

D10.8.3 Hepatitis B virus.

D10.8.4 Hepatitis C virus.

D10.8.5 Human T cell lymphotropic virus, type I.

D10.8.6 Human T cell lymphotropic virus, type II.

D10.8.7 *Treponema pallidum* (syphilis).

D10.8.8 Any additional agents required by Applicable Law at the time of release of the CB unit.

D11 MATERNAL TESTING

D11.1 The maternal blood sample obtained within seven (7) days before or after collection of the CB unit shall be tested for evidence of infection by the following communicable disease agents utilizing assays required for volunteer tissue donations and according to Applicable Law:

D11.1.1 Human immunodeficiency virus, type 1.

D11.1.2 Human immunodeficiency virus, type 2.

D11.1.3 Hepatitis B virus.

D11.1.4 Hepatitis C virus.

D11.1.5 Human T cell lymphotropic virus, type I.

D11.1.6 Human T cell lymphotropic virus, type II.

D11.1.7 *Treponema pallidum* (syphilis).

D11.1.8 Cytomegalovirus.

D11.1.9 If required by Applicable Law, the maternal blood sample obtained within seven (7) days before or after collection of the CB unit shall also be tested for evidence of clinically relevant infection by the following disease agents:

D11.1.9.1 West Nile Virus.

D11.1.9.2 Trypanosoma cruzi (Chagas' Disease).

D11.2 The CBB shall have a written policy to address positive or indeterminate results found during the screening process and/or laboratory testing of maternal samples.

D11.3 Positive or indeterminate test results, excluding cytomegalovirus, shall be communicated to the mother and/or her physician according to Applicable Law.

D11.4 All maternal samples should have negative or non-reactive test results with the exception of Cytomegalovirus antibody, Hepatitis B core antibody, and *Treponema pallidum* (syphilis).

D11.4.1 If allowed by Applicable Law, maternal samples that are hepatitis B core antibody positive and are accepted shall be hepatitis B negative by DNA testing.

D11.4.2 If allowed by Applicable Law, maternal samples that screen positive for *Treponema pallidum* (syphilis) using a non-treponemal-specific screening test and are accepted shall be negative using a specific confirmatory test.

D11.5 Any CB units reactive for other agents shall be quarantined.

PART E: CORD BLOOD LISTING, SEARCH, SELECTION, RESERVATION, RELEASE, AND DISTRIBUTION STANDARDS

PART E: CORD BLOOD LISTING, SEARCH, SELECTION, RESERVATION, RELEASE, AND DISTRIBUTION STANDARDS

E1 GENERAL REQUIREMENTS

E1.1 There shall be designated facilities with adequate space for procedures and records related to CB unit listing, search, selection, reservation, release, and distribution.

E1.2 There shall be a defined process to prevent listing of directed allogeneic and autologous CB units for unrelated use.

E1.3 The CBB shall have policies and Standard Operating Procedures for the following at a minimum:

E1.3.1 Listing, search, selection, reservation, release, and distribution of CB units to Clinical Programs.

E1.3.2 Verification of confirmatory HLA typing of the CB unit.

E1.3.3 Verification that the infant donor and the recipient are different individuals in the case of complete HLA matches.

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

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 Reservation of a CB unit shall not be in place simultaneously for more than one potential recipient.

E1.6.2 The CBB shall notify all listing organizations in a timely manner when a CB unit is removed from inventory.

E2 REVIEW AND LISTING OF CORD BLOOD UNITS

E2.1 The CBB shall have policies and Standard Operating Procedures for the comprehensive review of unrelated allogeneic CB unit records prior to listing a CB unit, including at a minimum:

E2.1.1 From the CB unit after processing prior to cryopreservation:

E2.1.1.1 Total nucleated cell count.

E2.1.1.2 Nucleated red blood cell count.

E2.1.1.3 Total number of CD34 cells.

E2.1.1.4 Viability and/or potency as measured by viable CD34 cells and/or CFU.

E2.1.1.5 CBC with differential.

E2.1.1.6 Microbial cultures.

E2.1.2 ABO group and Rh type.

E2.1.3 HLA type at a minimum of two digits.

E2.1.4 Hemoglobinopathy, if available.

E2.1.5 Infant donor's ethnicity/race.

E2.1.6 Infant donor's gender.

E2.1.7 Infant donor's physical examination.

E2.1.8 Maternal risk factors for transmission of communicable disease.

E2.1.9 Maternal communicable disease testing results.

E2.1.10 Family medical history for transmissible genetic and malignant diseases.

E2.1.11 Consents.

E2.1.12 Processing and cryopreservation parameters.

E2.2 Unrelated CB units shall be made available for search on a national registry and/or the CBB's registry only after testing and medical review has been completed.

E2.3 The CBB shall have policies and Standard Operating Procedures for the comprehensive review of directed allogeneic and autologous CB units prior to release.

E3 CORD BLOOD UNIT SELECTION AND RELEASE FOR ADMINISTRATION

E3.1 The CBB shall retain indefinitely documentation of requests for CB units, requests for reference samples and maternal samples, requests for and results of testing, and 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 type and, if possible, cell viability.

E3.2.1 If a contiguous segment is no longer available, another validated method shall be used to identify the CB unit.

E3.2.2 Any histocompatibility discrepancy shall be resolved and communicated to the registry and the Clinical Program.

E3.2.3 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.

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 From the CB unit after processing prior to cryopreservation:

E3.3.1.1 Total nucleated cell count.

E3.3.1.2 Nucleated red blood cell count.

E3.3.1.3 Total number of CD34 cells.

E3.3.1.4 Viability and/or potency as measured by viable CD34 cells and/or CFU.

E3.3.1.5 CBC with differential.

E3.3.2 Microbial cultures from the CB unit after processing prior to cryopreservation.

E3.3.2.1 For directed allogeneic and autologous cord blood administration, antimicrobial sensitivities shall be provided if positive microbial tests are documented in the CB unit record.

E3.3.3 ABO group and Rh type.

E3.3.4 All HLA Class I and II typing results, including prior results.

E3.3.4.1 A minimum of four digits shall be provided for DRB1.

E3.3.5 Hemoglobinopathy testing results.

E3.3.6 Any testing performed from a contiguous segment.

E3.3.7 Communicable disease testing results performed on the maternal sample and, if performed, on the CB unit.

E3.3.8 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.

E3.3.8.1 History of malignant disease in a first degree relative of the infant donor shall be disclosed to the Clinical Program.

E3.3.9 The method of CB unit processing.

E3.3.10 Any variances in collection, processing, testing, cryopreservation, storage, and/or transport or shipping procedures that may influence the integrity and/or quality of the CB unit.

E3.3.11 Physical characteristics of the CB unit, including at a minimum the number and type of bags or compartments used for storage.

E4 CORD BLOOD UNIT DISTRIBUTION TO A CLINICAL PROGRAM

E4.1 The CBB shall obtain a written or electronic request from the transplant physician, designee, or registry for distribution of the CB unit.

E4.2 The CBB Director or designee shall conduct a comprehensive record review prior to distribution of a CB unit to a Clinical Program and document this review in accordance with Applicable Law.

E4.3 When the maternal medical and/or genetic screening history indicates potentially transmissible disease or when there is a positive or indeterminate communicable disease test result:

E4.3.1 The CB unit shall not be released unless the CBB Director or Medical Director gives specific authorization for release of the nonconforming CB unit in compliance with Applicable Law and documents the rationale for such authorization.

E4.3.2 There shall be documentation of the consent to use the nonconforming CB unit from the transplant physician.

E4.3.3 CB units deemed nonconforming as a result of donor screening or testing for risk for transmission of communicable disease shall be labeled with the appropriate biohazard and warning labels detailed in Appendix II, Modified Circular of Information Biohazard and Warning Labeling Table.

E4.4 At the time of distribution to a Clinical Program, the CB unit bag shall be labeled as required in Appendix I, Cord Blood Unit Labeling Table.

E4.5 A Circular of Information 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 If the Clinical Program lacks experience in handling CB units, a practice CB unit should be offered.

E4.6.1 The practice CB unit shall be clearly labeled as a CB unit not intended for administration.

E4.7 The CB unit should be received by the Clinical Program prior to initiation of the recipient's preparative regimen.

E5 TRANSPORTATION AND SHIPPING OF CRYOPRESERVED CORD BLOOD UNITS

E5.1 Procedures for transportation and shipping of cryopreserved CB units shall be designed to protect the integrity of the CB unit and the health and safety of personnel.

E5.2 The transit time between the CBB and other facilities shall be minimized.

E5.2.1 There shall be 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^{o}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 a device 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 The lid of the dry shipper and the lid of the outer container shall be secured.

E5.3.5 The outer container shall be labeled with the information required in Appendix I, Cord Blood Unit Labeling Table.

E5.4 The CBB shall have a written policy to obtain the following data from the receiving facility about the CB unit upon receipt:

E5.4.1 Date and time of receipt.

E5.4.2 Integrity of the dry shipper.

E5.4.3 Internal temperature of the dry shipper.

E5.4.4 Integrity of the CB unit.

E5.5 Once an unrelated CB unit has left the CBB premises, it shall not be returned to the general CBB inventory.

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 A list identifying each CB unit and document enclosed in a package shall be included.

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.

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.

E7 CLINICAL OUTCOME DATA

E7.1 For every CB unit released for administration, the CBB shall maintain details of clinical outcome as necessary to ensure that the procedures in use in the CBB provide a safe and effective product.

E7.1.1 The CBB shall obtain this information directly from the Clinical Program or, if utilized, through a registry or outcomes database.

E7.2 The CBB shall have a policy or procedure to obtain the following information within the recommended time period for every CB unit released for administration:

E7.2.1 Viability and cell yield results on the thawed CB unit should be reported to the CBB.

E7.2.2 Adverse events associated with administration of the CB unit should be reported to the CBB promptly and within six weeks of transplant.

E7.2.3 Time to neutrophil and platelet engraftment should be reported to the CBB within six months of transplant.

E7.2.4 Survival rates should be reported to the CBB annually at a minimum.

E7.2.5 For allogeneic CB units only, data should include chimerism and GVHD results that should be reported to the CBB annually at a minimum.

E7.2.6 In the case of more than one graft product used for administration, the CBB should collect and document that information and, if possible, which donor engrafted.

APPENDICES

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Appendix I

Cord Blood Unit Labeling Table

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	F	F		F	F	
Proper name[2]	F	F	F	F	F	
Product modifiers and manipulations[2]				C	C	
Statement "Directed Allogeneic Donor" or "Autologous Use Only" [1]	T	T		F	F	
Collection site identifier		F				
Date of collection		F		C	C	
Time of collection and time zone, if different from the CB Processing Facility		C				
Name and volume or concentration of additives				C	C	
Name and volume or concentration of anticoagulants		F		C	C	
Recommended storage temperature		T		F	F	
Donor name (Directed Allogeneic and Autologous CB units)[1]		F		F	F	
Recipient family or individual name and unique identifier, if known[1]		F		F	F	
Recipient's name and unique identifier (if unknown after processing prior to cryopreservation)					T	
Volume or weight of the CB unit at the end of collection				C	C	
Volume or weight of the CB unit at the end of processing				C	C	
Date of cryopreservation				C	C	
ABO group and Rh type				C	C	
HLA phenotype				C	C	
Number of nucleated cells post processing				C	C	
Gender of CB unit infant donor				C	C	
Identity of the CBB[3]				F	F	
Statement "Properly Identify Intended Recipient and Product"					T	
Statement "For Use By Intended Recipient Only" (Allogeneic CB units)[1]					T	
A statement indicating that leukoreduction filters should not be used					T	
Statement "Do Not Irradiate"					T	
Statement "For Nonclinical Use Only"[1]					T	
Biohazard legend and/or warning labels (see Appendix II, Modified Circular of Information Biohazard and Warning Labeling Table)[1]		C		C	C	
Donor eligibility summary. See Appendix III.					C	
Date and time of distribution					C	F
Shipping facility name, address, phone number			F			F
Receiving facility name, address, phone number			F			F
Identity of person or position responsible for receipt of the shipment			F			F
Statement "Do Not X-Ray"[4]			F			F
Statement "Medical Specimen", "Handle With Care"[4]			F			F
Statement indicating Cord Blood for Transplantation						F
Shipper handling instructions[4]			F			F

[1]If applicable.
[2]Product proper names, modifiers, 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
[3]If there are CBBs of the same name in multiple countries, the identifier must distinguish between the CBBs on the label.
[4]If CB unit is shipped.

F=Affix, T=Attach or Affix, C=Accompany or Attach or Affix; the chart has minimum requirements only. A CBB may choose to be more inclusive.

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Appendix II Modified Circular of Information Biohazard and Warning Labels

			Status				Product Labels				
	Title 21 CFR Citation [F]	All Donor Screening and Testing Completed	Abnormal Results of Donor Screening	Abnormal Results of Donor Testing	Donor is resident in country on USDA [E] BSE list OR Testing performed in non-CLIA-certified laboratory.	Urgent Medical Need	Biohazard Legend [per 21 CFR 1271.3(h)]	For Autologous Use Only	Not Evaluated for Infectious Substances	WARNING: Advise patient of communicable disease risks	WARNING: Reactive test results for (name of disease agent or disease)
Donor Eligibility Determination Required [21 CFR 1271.45(b)]											
1	Allogeneic donors with incomplete donor eligibility determination [A,B]	1271.60	No	No	No	Yes			X	X	
2	Allogeneic donors found ineligible										
	A first-degree or second-degree blood relative [C]	1271.65(b) 1.i	Yes	No/Yes	Yes	NA	X			X	X
	A first-degree or second-degree blood relative [C]	1271.65(b) 1.i	Yes	Yes	No	NA	X			X	
	Unrelated donor	1271.65(b) 1.iii	Yes	No/Yes	Yes	Yes	X			X	X
	Unrelated donor	1271.65(b) 1.iii	Yes	Yes	No	Yes	X			X	
	Unrelated donor (USA Regulation [G])		Yes	No	No	Yes	X			X	
Donor Eligibility Determination Not Required [21 CFR 1271.90(a)]											
3	Autologous donors [D]	1271.90(a)(b)									
	Autologous donor	1271.90(a)(1)(2)	No	No	No			X	X		
	Autologous donor	1271.90(b)(1)(3)	Yes	No/Yes	Yes		X	X			X
	Autologous donor	1271.90(b)(1)(3)	Yes	Yes	No		X	X			

A. The donor eligibility must be finalized during or after the use of the cellular therapy product. The results must be communicated to the treating physician [21 CFR 1271.60(d)4].

B. Abnormal results of any screening or testing requires labeling as in item 2 in this table (21 CFR 1271.65 applies).

C. Notification of the recipient's and donor's physicians of abnormal screening and/or testing results is required.

D. Any abnormal donor screening or testing results (even though neither screening nor testing is mandated for this group of donors) require appropriate labeling [21 CFR 1271.90(b)].

E. USDA – United States Department of Agriculture.

F. USA Federal Register, Code of Federal Regulations, Part 1271, Human Cells, Tissues, and Cellular Based Products, Revised January 1, 2004.

G. Applies to any cord blood unit collected, processed, stored, transported or transplanted in the US.

Modified table from the *Circular of Information for the Use of Cellular Therapy Products*, AABB et al. 2009. This table was modified to account for issues unique to CB banking. For the current version, visit www.factwebsite.org.

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ACCOMPANYING DOCUMENTS AT DISTRIBUTION TO A CLINICAL PROGRAM

CB units shall be accompanied upon leaving the CBB with the elements detailed in the following table at a minimum as required by Applicable Law[1]:

Documentation	Allogeneic Donor-Eligible	Allogeneic Donor-Ineligible	Allogeneic Donor-Incomplete	Autologous Donor
Statement that the donor has been determined to be either eligible or ineligible, based upon results of donor screening and testing	X	X		
Summary of records used to make the donor-eligibility determination[2]	X	X		
Name and address of the establishment that made the donor-eligibility determination	X	X		
Listing and interpretation of the results of all communicable disease screening and testing performed	X	X	X	X
Identification of the laboratory performing communicable disease testing meeting regulatory requirements.[3]	X	If applicable	If applicable	If applicable
Documentation of notification of the physician using the product of the results of all testing and screening	X	X	X	X (testing only)
Statement that the donor-eligibility determination has not been completed			X	
Listing of any required screening or testing that has not yet been completed			X	
Documentation that 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.			X	
Instructions for use to prevent the introduction, transmission, or spread of communicable diseases	X	X	X	X

[1] All elements are required for CB units manufactured in or designated for use in the U.S.

[2] Access (electronic or otherwise) to the source documents by the distributing facility and/or receiving facility is sufficient.

[3] Includes laboratories certified under CLIA of 1988, as amended from time to time, or those that have met equivalent requirements as determined by the Centers for Medicare and Medicaid Services.

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INDEX

F

G

H

I

L

M

N

O

P

Q

R

S

T

U

V

W

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