



FOUNDATION FOR THE  
ACCREDITATION OF  
CELLULAR THERAPY

AT THE UNIVERSITY OF NEBRASKA MEDICAL CENTER

## **6<sup>th</sup> Edition NetCord-FACT International Standards for Cord Blood Collection, Banking, and Release for Administration Summary of Changes**

This document summarizes the major changes made in the sixth edition of the *NetCord-FACT International Standards for Cord Blood Collection, Banking, and Release for Administration*. This summary does not include all changes made to the Standards; reorganization or clarified verbiage is not included unless considered to be a significant change. Refer to the final Cord Blood Standards and the accompanying Accreditation Manual for all requirements.

### **Significant Changes**

#### **1. CB Unit Specification Requirements**

- a. The sixth edition requires that CB units stored for clinical administration meet certain specifications. (D8.2)
  - i. Required specifications are outlined in Appendix V.
  - ii. Separate requirements exist for unrelated and related CB units.
    1. For related CB units, if specifications are unmet, the CBB at a minimum must follow its processes for deviations and nonconforming units in the event a customer insists on storage.

#### **2. Testing Requirements**

- a. Appendix IV contains the detailed testing requirements similar to previous editions. Several changes were made to the requirements as outlined below. This list does not include every instance in which a test must be performed. Review the appendix for complete requirements.
- b. Total Nucleated Cell Count should be performed on a thawed segment or thawed representative sample prior to release to the Clinical Program.
- c. Total CD34 must be performed post processing prior to cryopreservation.
- d. Total Viable CD34 should be performed on a thawed segment or thawed representative sample prior to release to the Clinical Program.
- e. % Viability of CD45 must be performed on a thawed segment or thawed representative sample prior to release to the Clinical Program.
- f. % Viability of CD34 must be performed post processing prior to cryopreservation and on a thawed segment or thawed representative sample prior to release to the Clinical Program.
- g. CFU or other validated potency assay should be performed post processing prior to cryopreservation and must be performed on a thawed segment or thawed representative sample prior to release to the Clinical Program.

3. Accreditation of Human Leukocyte Antigen (HLA) Typing Laboratories (B5.6)
  - a. Prior editions of Standards have required accreditation by American Society for Histocompatibility and Immunogenetics (ASHI), European Federation for Immunogenetics (EFI), or equivalent. Due to the difficulty of defining “equivalent,” a joint FACT/NMDP consultative committee of histocompatibility experts established guidelines for appropriate standards and accreditation for HLA laboratory services.
  - b. If a CBB wishes to use an HLA laboratory accredited by an organization other than ASHI or EFI, that accrediting organization must demonstrate that it meets the guidelines established by this committee.
  - c. An accredited CBB contemplating a change in HLA laboratory service provider must confirm appropriateness of accreditation prior to discontinuing services of an ASHI- or EFI-accredited HLA typing laboratory.
4. Scope of Standards
  - a. The scope of the Standards includes only the use of cord blood for clinical use.
  - b. Collection of Cord Tissue
    - i. For cord tissue storage, these Standards only apply to tissue samples retained for testing or research purposes. Collection and storage of cord tissue for therapeutic intent fall under the scope of the FACT Common Standards for Cellular Therapies.
    - ii. The Standards explicitly added “for testing” to clearly state why cord tissue is referenced. (B5.9.2)
  - c. The Cord Blood Bank (CBB) must have a policy or procedure to request the following information (in addition to previous requirements) for every CB unit released for administration for hematopoietic reconstitution: (E7.1)
    - i. Viable nucleated cell yield results on the thawed CB unit. (E7.1.1)
    - ii. Complaints associated with the CB unit. (E7.1.2)
    - iii. Microbial screening. (E7.1.7)
    - iv. Administered cell dose. (E7.1.8)
  - d. The CBB must have a policy to request outcome data that is relevant to other uses for which the CB unit was released. (E7.2)

### **Changes Throughout the Standards**

5. Policies and Standard Operating Procedures (B3, C3, D2)
  - a. Part B now includes all Standard Operating Procedures (SOPs) required in each section of the Standards. This reflects the CBB’s responsibility to ensure SOPs exist and are appropriate for all phases of CB collection, banking, and release for administration.
  - b. CBBs may choose to employ a single SOP at all sites or may utilize different SOPs at different sites.
6. Facilities and Safety (B4, C1.7, D1.6)
  - a. Facilities and safety requirements were reorganized to reduce ambiguity regarding which safety requirements apply to administrative facilities, collection sites, and processing facilities.
  - b. Administrative facilities represent a lower risk than other locations. Only the risks applicable are listed in B4.

- c. CB Collection Sites may not be completely under the control of the CBB; however, there must be processes in place that utilize universal precautions and are designed to minimize risks to the health and safety of employees, volunteers, and visitors, including at least: (C1.7)
  - i. Bloodborne pathogens. (C1.7.1)
  - ii. Hand washing and/or decontamination. (C1.7.2)
  - iii. Chemical hazards. (C1.7.3)
  - iv. Latex allergy. (C1.7.4)
- d. CB Processing Facility requirements for environmental conditions more explicitly list what conditions must be considered. (D1.6)
  - i. Conditions that may affect the safety and potency of CB units include temperature; humidity; ventilation; and air pressure, filtration and classification.
  - ii. The acceptable parameters must be defined. The sixth edition clarifies this requirement by stating that, as appropriate for the degree of classification, those parameters must be controlled, monitored, and recorded to demonstrate ongoing compliance.
- e. Liquid nitrogen has previously been listed as a risk to be mitigated; however, it has been interpreted to include only the risk of contact. The sixth edition specifically recommends that oxygen levels be monitored wherever liquid nitrogen is in use. (D1.7.5)

## **Changes by Section**

### *Part B Cord Blood Bank Operational Standards*

#### **7. General Requirements**

- a. Educational, promotional, and recruitment materials (B1.6, B2.7.1.5) must be supported by scientific evidence. This requirement is not new, but was made more specific and detailed to clearly delineate the types of materials to which the Standard applies. Because cord blood banking is promoted directly to lay people, CBBs have an obligation to truthfully describe the potential uses of cord blood units for various diseases.

#### **8. Quality Management**

- a. The Quality Unit Supervisor is now called the Quality Unit Manager throughout the Standards.
- b. Required services to be covered by written agreements when in use now explicitly include donor screening and testing, processing, and storage in addition to others. (B2.4.1)
- c. Change control now requires an assessment of the need to verify or validate the change. (B2.6.5)
- d. CBBs must perform an audit of records and assessment of record review to identify recurring problems, potential points of failure, or need for process improvement. (B2.11.3.1)
- e. Audit results must now be shared with the Quality Unit Manager in addition to the appropriate Director and/or Medical Director, manager of the area audited, and other relevant staff. (B2.11.5)
- f. The Quality Unit must also review all errors, accidents, biological product deviations, adverse events, variances, and complaints in a timely manner. (B2.12.5.3)

- g. Additional outcome analysis requirements include:
  - i. Suboptimal results and complaints must be investigated. (B2.16.3)
    - 1. One of the most important aspects of outcome analysis is evaluating the cause of suboptimal results. Although this was always expected of CBBs, the Standards now list these separately for emphasis.
  - ii. Outcome data must be trended to identify opportunities for improvement. (B2.16.4)
    - 1. In general, CBBs adequately review outcomes related to individual CB units, but several have been cited for not reviewing outcome data in aggregate to evaluate the cord blood banking program as a whole.
    - 2. Trending outcome data over time, using all cord blood units released for administration, enables CBBs to identify systemic issues that may result in suboptimal results.

## 9. Cord Blood Bank Operations

- a. The CBB Medical Director must give specific authorization to accept CB units if the genetic or medical history of a first-degree relative of the infant donor is unknown, in accordance with Applicable Law. (B5.5.4.1)
- b. Specific reference to the issue of CB units with unavailable medical history is new in this edition, and is relevant in cases such as sperm or egg donor, absent father, etc. If allowed by Applicable Law, the CBB Medical Director may decide if the incomplete genetic or medical history precludes banking of the CB unit.

## 10. Coding and Labeling of Cord Blood Units

- a. ISBT 128 Coding and Labeling. (B6.1.2)
  - i. The fifth edition required organizations to have a plan for ISBT 128 coding and labeling technology implementation. The sixth edition requires that organizations be actively implementing ISBT 128 coding and labeling technologies.
  - ii. "Actively implementing" could be demonstrated by registration with ICCBBA, identification or creation of appropriate product codes, label designs, label validation, and/or use of scanned information.
- b. A system for label reconciliation must be employed to prevent mix-up of labels and also to detect when a label was used for an incorrect CB unit. Label reconciliation applies to any label that includes unique identifier(s) or name(s). (B6.2.2)
- c. Barcoding may negate the need for verification of label information by two people. The verification now may be conducted by two qualified people or by one qualified person using a validated process. (B6.3.2.4)

## 11. Inventory Transfer

- a. Although transfer of inventory is not typically anticipated, CBBs must develop and maintain a plan for actions to take in the event they do transfer CB units or an entire inventory to another bank. (B10.1)
  - i. Section B10 was edited to clarify that a plan is required even if no transfer is expected.
  - ii. Written agreements for the transfer of inventory must specify that FACT-NetCord accreditation does not transfer with the inventory. (B10.2.1)

## 12. Documents and Records Requirements

- a. Exported CB unit records must be in a language understood by the importing organization or translated to English. Translation to English was previously required for export to the US. The standard was broadened for international applicability. (B11.4.1)
- b. For validation of electronic record systems, the Standard was clarified to state that validation of systems development includes verification of calculations and algorithms. (B11.9.6.1)

## 13. Interruption of Operations at Established Sites

- a. The standard was clarified to emphasize that the CBB must have a plan in the event any operation must be discontinued. The requirements were broadened and specified. (B12.1)
- b. If a CBB discontinues banking of new CB units: (B12.3)
  - i. There must be a process to continue the stability program. (B12.3.2)
  - ii. There must be a process to distribute CB unit contiguous segments and samples for testing, including pre-release testing. (B12.3.3)
  - iii. For related CBBs, the staff must maintain communication with donor families, if applicable. (B12.3.6)

### *Part C Cord Blood Donor Management and Collection Standards*

## 14. Cord Blood Collection Personnel Requirements (C2)

- a. Because of the variety of collection models, the sixth edition Standards are less prescriptive regarding the methods and/or personnel involved in maintaining a defined line of communication between the collection site and the CBB. Regardless of the collection model, there must still be an explicit method of communication between the two facilities.
- b. Training requirements for personnel at the Collection Site were reorganized and clarified to separate requirements for professionals directly responsible for collection from training required of those with different roles in the collection process, such as history review or obtaining maternal blood samples.

## 15. Informed Consent (C4)

- a. Throughout this section, standards were reorganized to accommodate the variety of methods used by CBBs to obtain and document informed consent. Consent requirements for all donations were delineated, and distinguished from those requirements specific for unrelated donations or unique to related donations.
- b. References to an agreement between the mother and the CBB were added throughout the section to provide clarity that these agreements could serve a role in the consent process.
  - i. CBBs collecting only related donor units often perform the informed consent process in conjunction with the written agreement, and this language is intended to enhance comprehension of the requirements.
  - ii. All potential CB banking participants, including those involved in related donor banking, must be fully informed of the banking processes, the risks and benefits, and be allowed to ask questions, decline to participate, or to affirm agreement to bank the infant donor's cord blood.
- c. The CBB must only perform steps in the CB banking process for which it has informed consent or a signed agreement from the mother. Testing was added to the list of steps that must have specific consent or be included in a signed agreement. (C4.3, C4.3.3)

- d. New requirements for information to be provided include:
  - i. Explicitly stating that both maternal and CB unit samples will be stored for future testing. (C4.5.9)
  - ii. If the intended use of the unit is unknown, donor eligibility must be determined. (C4.8)

#### 16. Maternal and Infant Donor Evaluation

- a. Any abnormal result relevant to the health of the maternal or infant donor must be reported to the relevant healthcare provider, maternal donor, and governmental authority according to Applicable Law. The previous standard required only notification of relevant healthcare provider OR the maternal donor. (C5.1.6)
- b. Maternal and infant donor screening must include a medical history, review of medical records, and review of physical examination findings. (C5.2)

#### 17. Cord Blood Collection

- a. *In utero* collection requirements were modified to allow health care professionals more decision-making authority. (C6.2)
  - i. In the fifth edition, *in utero* CB collections were only allowed to occur in uncomplicated deliveries as determined by the licensed health care professional responsible for the delivery. In the sixth edition, this requirement is limited to *in utero* CB collections for unrelated donations.
  - ii. CB units collected *in utero* at less than 34 weeks gestation must be based on an evaluation of infant donor safety by the licensed health care professional responsible for the delivery. Previously, collection at less than 34 weeks gestation was not allowed for unrelated donations. The sixth edition leaves this decision up to the health care professional following an evaluation of infant donor safety. (C6.2.3)
- b. CB units, associated samples, and maternal samples at collection sites must be maintained at a defined temperature range. (C6.7.1)
- c. The chain of custody of the CB unit must be maintained from collection to receipt at the CBB. (C6.8)

#### 18. Transportation and Shipping of Unmanipulated Cord Blood Units Between the Cord Blood Collection Site and the Cord Blood Processing Facility

- a. The process for transport and shipping must be validated to maintain a designated temperature range in the immediate environment of the CB unit. (C7.5.2)
- b. When a CB unit is shipped, the temperature inside the immediate environment must be continuously monitored, or the unit must be shipped in a rigorously validated container. (C7.5.3)
  - i. The term “rigorously” was intentionally added to stress that compliance with this option requires an extremely robust validation that accounts for several worst-case scenarios (i.e., delays, temperature excursions) in all modes of transportation or shipping used (e.g., car, airplane).
  - ii. It will be incumbent on the CBB to demonstrate through data and validation summaries to the inspector and Accreditation Committee that the container was rigorously validated.
  - iii. Specific validation requirements are listed in the Accreditation Manual.
  - iv. The CBB Must have acceptance criteria for all units prior to processing.

- v. If related donor units are received that do not meet acceptance criteria, the CBB must notify the family donors.

#### *Part D Cord Blood Processing Standards*

##### 19. Cord Blood Processing

- a. For related CB units, the fifth edition required a signed agreement with the donor family for collection, processing, testing, and storage of the CB unit. The sixth edition also requires that disposal be included in the agreement. (D3.1.3).
- b. Processing and cryopreservation of CB units must be performed according to Standard Operating Procedures validated to result in acceptable potency in addition to acceptable viability and recovery. (D3.2.4)

##### 20. Samples

- a. When a CB unit is initially requested, a minimum of one (1) contiguous segment must be used to verify the results of HLA typing. Sixth edition Standards require HLA verification typing when a CB unit is initially released, compared to the fifth edition requirement at the time of release. (D4.1.1.2)
- b. When a CB unit is initially requested for clinical use, potency must be tested in accordance with the Testing Requirements table in Appendix IV and must meet the specifications outlined in the Specification Requirements table in Appendix V. (D4.1.1.3) These are new requirements.
- c. At the time of removal for testing, one (1) qualified person using a validated process or two (2) qualified people must verify the identity of the segment. (D4.1.1.4)
- d. The Standards define representative and retention samples to clarify that the retention sample is not intended to be used for routine testing, but is intended to be maintained after the unit was released for potential future uses.
  - i. Representative sample: Aliquot of the final cord blood product that is stored under the same conditions as the cord blood unit, and can be used to test for viability, potency, or stability.
  - ii. Retention sample: Aliquot of the final cord blood unit saved for future use, such as investigation of adverse events or retroactive quality control activities.
- e. To address the newly-defined representative samples, the sixth edition states that representative samples (in addition to retention samples) intended for viability or potency analysis must be stored under the same conditions as the CB unit. (D4.1.2.1)
- f. Samples of plasma from the CB unit must be collected, rather than "serum or plasma." Collection of serum alone is no longer in compliance with the Standards, although CBBs may choose to collect serum in addition to the required minimum total volume of 3.6 mL of plasma. (D4.1.3)
- g. Use of heparin in plasma samples is no longer restricted. (D4.1.3)

##### 21. Cryopreservation

- a. Total Nucleated Cell (TNC) recovery should be  $\geq 60\%$  after processing prior to cryopreservation. (D5.1.1)
- b. CB units must be placed into individual metal canisters for protection; a single canister may not be used for multiple units. (D5.3)

## 22. Conditions for Storage

- a. Samples, in addition to CB units, must be stored in a secure area. (D6.1)
- b. Warming events at any time after cryopreservation must be minimized. The prior requirement was "at any time after the process of storage," which led to some confusion. (D6.5.2)
- c. The details and purpose of the stability program are expanded and codified in the sixth edition.
  - i. There must be a written stability program to assess cryopreserved CB units for post-thaw microbial contamination, potency, and integrity. (D6.6)
    1. Because units cannot easily be tested prior to release, the CBB must develop a stability program that annually tests units of various storage duration and manufacturing methods for viability and potency.
    2. The length of unit storage is unknown, so data must be accumulated to demonstrate that the conditions of cryopreservation and storage results in units that can provide acceptable hematopoietic reconstitution.
  - ii. A minimum of three (3) units per manufacturing method must be assessed annually. (D6.6.1)

## 23. Monitoring and Alarm Systems (D7.3)

- a. These standards were clarified to require maintenance of liquid nitrogen levels when units are stored fully immersed in liquid nitrogen, and monitoring and recording of temperature when units are not fully immersed in liquid nitrogen. The intent of the standard is not changed.

## 24. Disposition

- a. The CBB must have defined criteria for disposition of a CB unit. Previously, a policy for these functions was required. Under the sixth edition, a policy would be acceptable only if specific defined criteria are included. (D8.1)
  - i. CB units released for listing on the registry now also must meet defined criteria. (D8.1.1)
  - ii. For CB units that are discarded, persons authorized to approve discard must be defined. (D8.1.5)

## 25. Disposal

- a. Cryopreserved related CB units lacking a signed consent must be maintained in quarantine status until consent has been obtained. (D8.4.2.2)

## 26. Cord Blood Unit Testing

- a. For CBC differentials, defined parameters for monocytes are no longer required. (D9.3.1)

## *Part E Cord Blood Listing, Search, Selection, Reservation, Release, and Distribution Standards*

## 27. Review of Cord Blood Unit Records

- a. The nature of ineligible CB units must be disclosed to the registry and/or the requesting party. (E2.3)

## 28. Cord Blood Unit Selection and Release for Administration

- b. The CBB must disclose to the Clinical Program if the genetic or medical history of a first-degree relative is unknown. (E3.3.4.1)

## Appendices

### 29. Key Personnel Requirements (Appendix 1)

- a. In the fifth edition Cord Blood Standards, the requirements for the CBB Director, CBB Medical Director, CB Collection Director, CB Processing Facility Director, and Quality Unit Manager were defined in Part B. In the sixth edition, these requirements are defined in a table in Appendix I.

### 30. Cord Blood Unit Labeling (Appendix II)

- a. The following label elements were changed from affixed to attached or affixed:
  - i. Partial label
    1. Unique numeric or alphanumeric identifier
    2. Proper name of product
  - ii. At completion of collection
    1. Collection site identifier
    2. Date of collection
    3. Donor name (Related CB units)
    4. Recipient family or individual name and unique identifier, if known
  - iii. At completion of processing prior to cryopreservation
    1. Donor name (Related CB units)
    2. Recipient family or individual name and unique identifier, if known
  - iv. At distribution to Clinical Program
    1. Donor name (Related CB units)
    2. Recipient family or individual name and unique identifier, if known
- b. The following label elements were changed from attached or affixed to accompanied:
  - i. At distribution to Clinical Program
    1. Statement "Properly Identify Intended Recipient and Product"
    2. Statement "For Use By Intended Recipient Only" (allogeneic CB units)
    3. A statement indicating that leukoreduction filters should not be used
    4. Statement "Do Not Irradiate"
    5. Statement "For Nonclinical Use Only"

### 31. Accompanying Documents at Distribution (Appendix III)

- a. This table was expanded to more completely describe the US regulations for documentation of incomplete donor eligibility.
- b. Instructions for reporting serious adverse reactions or events to the distributing facility was also explicitly added to Appendix III. This is required of all cellular therapy products regardless of donors' eligibility status.