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Effective Transition to the Seventh Edition NetCord-FACT International Cord Blood Standards

Presented by Paul Eldridge, PhD
Director, Cell GMP Facility
UNC Bone Marrow Transplant and Cellular Therapy Program

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Conflict of Interest Disclosure

The presenter has no conflict of interest with the subject matter.

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

Publication date: October 15, 2019

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Factors in Standards Revision

- New developments
  - Evidence-based
- Feedback from sixth edition
  - Standards
  - Accreditation
- Input from related
  - Organizations
  - Individuals

Major Content Changes

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ISBT 128 and Eurocode

Full implementation (B6.1.2)

- The Sixth Edition NetCord-FACT Standards required that organizations be actively implementing ISBT 128 at a minimum. The Seventh Edition Standards require that ISBT 128 or Eurocode be fully implemented. Appendix II was updated to convey requirements specific to both ISBT 128 and Eurocode. The changes are outlined in Appendix II below.

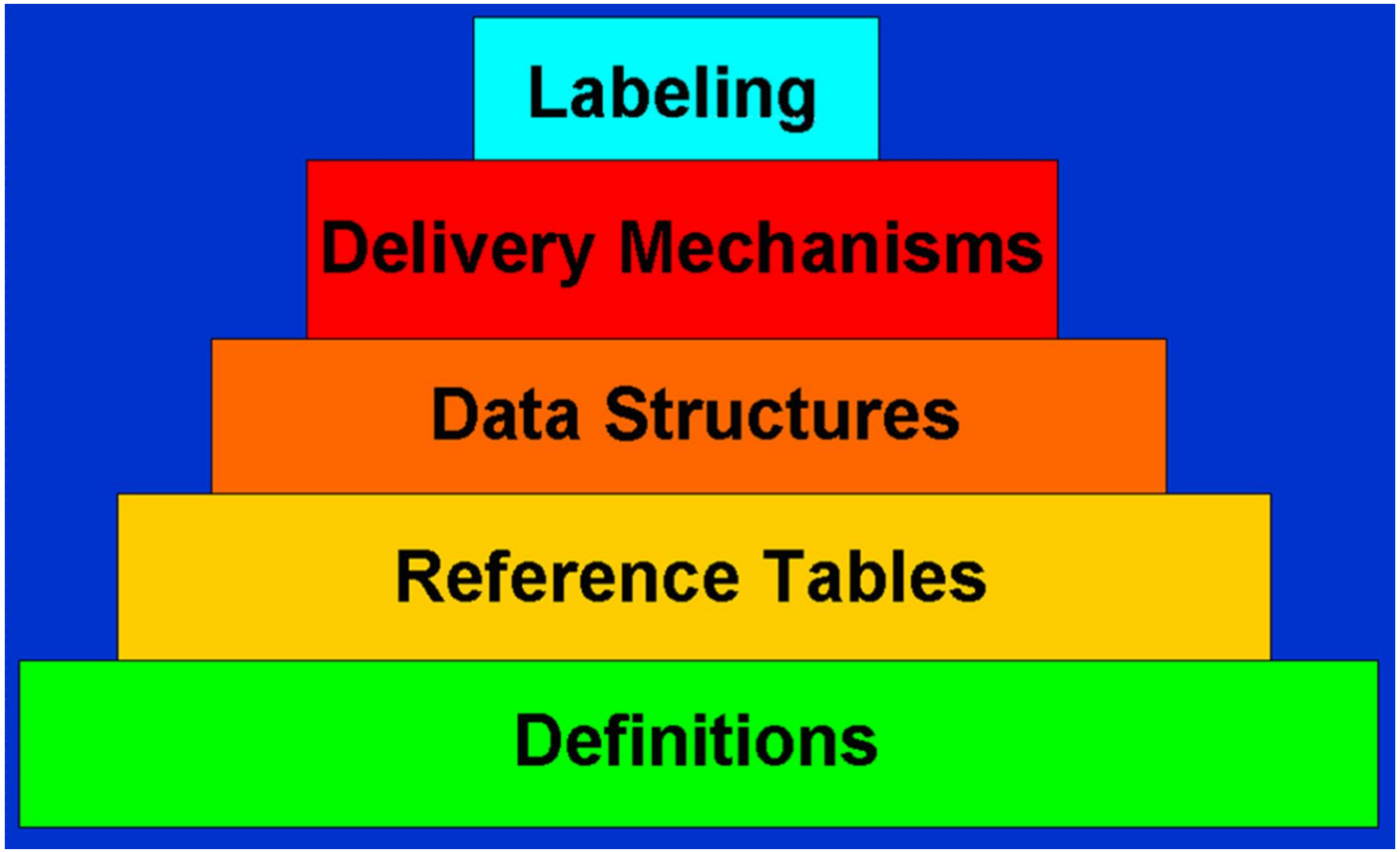
Partial Label at Distribution for Administration (A4, B6.6.5, Appendix II)

- The Seventh Edition Standards redefined the partial label used at the time of distribution for administration. A partial label must only be used if there are size constraints; otherwise, a full label must be applied.

Detached Segments (B6.2.6)

- In the Sixth Edition, integrally attached segments were recommended to be labeled with an identifier linking the segments to the applicable CB unit. In the Seventh Edition, detached segments are required to be labeled with an identifier linking the segments to the applicable CB unit.

ISBT 128 Information Hierarchy



APPENDIX II

CORD BLOOD UNIT LABELING[1]

Applicable standard	B6.6.4 C6.6	C7.6	B6.6.4 D3.3	B6.6.4 E4.5	B6.6.5	E5.3.6
Label Element	**At completion of collection**	**Outer container labeling at transport or shipping from collection**	**Post processing prior to cryopreservation**	**At distribution from the CBB to Clinical Program[7]**	**Partial label at distribution for administration[6]**	**Outer container labeling at distribution from the CBB to Clinical Program[8]**
Unique numeric or alphanumeric identifier	AF		AF	AF	AF	
Proper name of product[2]	AF		AF	AF	AF	
Product Code[2]			AF	AF	AF	
Product attributes (manipulations)[2]			AC	AC	AC	
Statement Related Donor[1]	AF		AF	AF	AF	
Statement "Autologous Use Only"[3]				AF	AC	
Statement "Caution: New Drug – Limited by Federal (or United States) law to investigational use."[6]				AC	AC	
Statement "Rx Only"[5] *(Rx = Prescription)*				AC	AC	
Collection site identifier	AC				AC	
Date of collection	AC		AC	AC	AC	
Time of collection and time zone, if different from the CB Processing Facility	AC				AC	
Name and volume or concentration of additives			AC	AC	AC	
Name and volume or concentration of anticoagulants	AF		AC	AC	AC	
Recommended storage temperature	AC		AF	AF	AC	
Donor name (Related CB units)[3]	AC		AT	AC	AC	
Recipient family or individual name and unique identifier, if known	AC		AT	AC	AC	
Recipient's name and unique identifier				AC	AC	
Volume or weight of the CB unit at the end of collection			AC	AC	AC	
Volume or weight of the CB unit at the end of processing			AC	AC	AC	
Date of cryopreservation			AC	AC	AC	
ABO group and Rh type				AC	AC	
HLA phenotype				AC	AC	
Number of nucleated cells post processing			AC	AC	AC	
Gender of CB unit infant donor			AC	AC	AC	
Identity of the CBB[4]			AF	AF	AC	
Statement "Properly Identify Intended Recipient and Product"				AC	AC	
Statement "For Use By Intended Recipient Only" (Allogeneic CB units)[3]				AC	AC	
A statement indicating that leukoreduction filters should not be used				AC	AC	
Statement "Do Not Irradiate"				AC	AC	
Statement "For Nonclinical Use Only"[3]				AC	AC	
Biohazard legend and/or warning labels (see B6.6.3)[3]	AC		AC	AC	AC	
Donor eligibility summary. See Appendix III.				AC	AC	
Date and time of distribution				AC	AC	AF

Testing and Specification Requirements

Changes to Appendix IV Testing Requirements

APPENDIX IV

TESTING REQUIREMENTS

	CB Samples						Maternal Samples
Test	Pre-processing	Post-processing prior to cryo-preservation	Any time prior to cryo-preservation	On an appropriate sample type at any time prior to listing	Thawed segment or thawed representative sample prior to release to the Clinical Program	On an appropriate sample type at any time prior to release	Obtained within seven (7) days before or after CB collection
Cell Count							
CBC with differential	X						
Total nucleated cell count		X			Should be performed		
Nucleated red blood cell count		X					
Total CD34		X					
Total Viable CD34		X			Should be performed		
Viability							
% Viability of Total nucleated cell ~~or % Viability of CD45~~		X			~~X~~		
~~% Viability of CD45~~					~~X~~		
% Viability of CD34		~~X~~			X		

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Testing and Specification Requirements Continued

Changes to Appendix V Specification Requirements for Cord Blood Units Stored for Clinical Administration

APPENDIX V

SPECIFICATION REQUIREMENTS FOR CORD BLOOD UNITS STORED FOR CLINICAL ADMINISTRATION

Test	Unrelated Specification		Related Specification	
	~~Fresh~~ Post-Processing prior to cryopreservation Sample	~~Post-Thaw Attached~~ Thawed contiguous segment or representative sample prior to release to the Clinical Program	~~Fresh~~ Post-Processing prior to cryopreservation Sample	~~Post-Thaw Attached~~ Thawed contiguous segment or representative sample prior to release to the Clinical Program
Total nucleated cell count	≥ 5.0×10^8		Enumerated	
Total nucleated cell recovery	Should be ≥60%		Should be ≥60%	
~~Total~~ Viability of total nucleated cell count	≥ 85%		≥ 70%	
Viable CD34 count	≥ 1.25×10^6			
Viability of CD34 cells	~~≥ 85%~~	≥ 70%	~~≥ 85%~~	~~≥ 70%~~
~~Viability of CD45 cells~~	-	~~≥ 40%~~	-	~~≥ 40%~~

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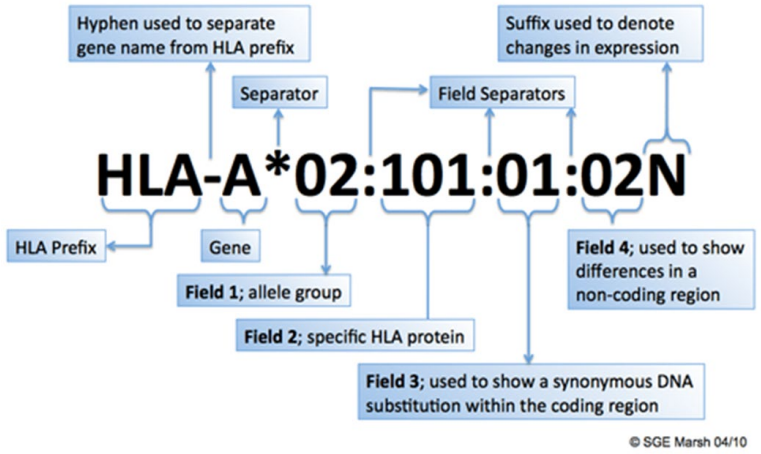
Accreditation of HLA Typing Laboratories (B5.6)

The College of American Pathologists (CAP) has been approved as an accrediting organization providing histocompatibility services appropriate for hematopoietic cellular therapy.

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



Changes Made to the Standards for Consistency

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Changes Made for Consistency

In the Seventh Edition, the following policies and SOPs were added to Part B for consistency:

a. Hand washing and sanitation. (B4.2.2)

b. Liquid nitrogen, including monitoring of oxygen levels. (B4.2.6)

c. Latex allergy. (B4.2.7)

d. Radiation safety, if applicable. (B4.2.8)

Sixth Edition supply and reagent standards B8.4, B8.4.1, B8.6, and B8.6.1 were combined to form one (1) standard in the Seventh Edition:

- Supplies and reagents that come into contact with the CB unit during collection, processing, or storage must be sterile and of the appropriate grade for the intended use. (B8.4)

Changes Made for Consistency Continued

In the Sixth Edition, a process to prevent the use of expired reagents and supplies was only explicit in Part C. In the Seventh Edition, this requirement was added to Part B:

- There shall be a process to prevent the use of expired reagents and supplies. (B8.10)

In the Sixth Edition (B1.5.1), the CBB must have an adequate number of qualified staff for its operations. In the Seventh Edition, the following standards were added to Part C and Part D for consistency:

- The CB Collection Site shall have adequate staff to perform collection activities. (C2.2)
- The CB Processing Facility shall have an adequate number of qualified staff for its operations. (D1.7)

Changes Made for Consistency Continued

In the Sixth Edition (B3.1.15), the CBB was required to establish and maintain policies or Standard Operating Procedures for acceptance criteria for CB unit receipt, processing, cryopreservation, and storage. In the Seventh Edition, the following requirement was added to Part D:

- Acceptance criteria for CB unit receipt, processing, cryopreservation, and storage. (D2.1.1)

Changes Specifically to: Part B Cord Blood Bank Operation Standards

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Quality Management (QM)

In addition to revising standards to explicitly and consistently state requirements, the following changes were made:

- The CBB Director or designee shall be responsible for the Quality Management Plan. (B2.2.1)
- Additional written agreement requirements include:
  - Agreements must be established with external parties providing critical services that could affect the quality and safety of the CB unit or health and safety of the infant donor and mother. (B2.4.1)
  - Agreements must have a defined effective date. (B2.4.3)
  - Agreements must be reviewed on a regular basis, at a minimum every two years. (B2.4.4)
- Review and approval of the audit plan, audit report, results, and conclusion by the CBB Director or designee and the Quality Unit Manager or designee. (B2.11.5)
- Follow-up audits of the effectiveness of corrective and preventive actions shall be performed in a timeframe as indicated in the investigative report. (B2.12.6.5)
- The Quality Unit Manager must review and report on quality management activities, at a minimum, quarterly. Meetings should have defined attendees, documented minutes, and assigned actions. Review findings must be reported to staff. (B2.18.1, B2.18.1.1)
- The annual report and documentation of the review findings must be made available to key personnel. (B2.19.1)

Policies and Standard Operating Procedures (SOPs)

In the Sixth Edition Standards, the CBB was required to maintain a detailed Standard Operating Procedures Manual that included a table of contents, and a standardized format for policies, SOPs, worksheets, and labels.

In the Seventh Edition, the requirement was changed to require a list of all controlled documents including the title and identifier. (B3.2)

Facility and Safety

Changes were made to facility requirements to include that the facility must provide adequate lighting, ventilation, sinks, and toilets, in addition to the current requirements of adequate size, construction, and location to maintain safe operation, prevent contamination, and promote orderly handling. (B4.1.1)

Equipment

Three new requirements were added to the equipment section:

1. The CBB must establish policies and SOPs for the management of critical equipment including identification, qualification, calibration, and maintenance. (B7.1)
2. There must be a mechanism to identify which piece of equipment was used for each CB unit. (B7.3.1)
3. Equipment decommissioning or disposition must be described and documented. (B7.9)

Supplies and Reagents

The following edits were made to the supplies and reagent standards:

Clarification edits

- Supplies and reagents that come into contact with the CB unit during collection, processing, or storage must be sterile and of the appropriate grade for the intended use. (B8.4)

New standards

- Where there are no suitable clinical or pharmaceutical grade reagents available, reagents shall undergo lot-to-lot functional verification and must include acceptance criteria to confirm that new lots perform as expected compared to the previous lots. (B8.4.1)
- Supplies and reagents must be quarantined until they have been determined to meet criteria for release from quarantine. (B8.8.1)

New standards

- An expiration date must be assigned to in-house prepared solutions or components. (B8.10.1)
- An expiration date must be assigned to the collection kit, and shall be consistent with the first item in the collection kit set to expire. (B8.10.2)

Inventory Transfer

The following new standards were added for inventory transfer:

- The written agreement must specify each party's responsibilities. (B10.2.2)
- For related CB units, the family should be made aware of the intent to transfer the units. (B10.3)

Changes to Part C: Cord Blood Donor Management and Collection Standards

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Personnel Requirements

Training on the collection procedure must cover each aspect of the CB collection process, and include:

- The collecting health care professional's initial and continuous training shall be documented. (C2.4.2)
- The minimum level of activity shall be specified to maintain competency. (C2.3.3)

Informed Consent

Two new requirements were added for discussing all aspects of participation in CB donation with the mother in a language and with terms that she understands.

- If an interpreter or translator is utilized, the identity of the interpreter or translator must be documented. (C4.2.1)
- Family members must not serve as interpreters or translators. (C4.2.2)

A new requirement was added for the CBB's policies for disposal of the CB units.

- The CBB's policies for disposition of related CB units in the event of cessation of operation. (C4.5.12.4)

Changes to Part D: Cord Blood Processing Standards

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Acceptance Criteria

Minor changes were made to the acceptance criteria standards to provide clarity. (D3.1.1, D3.1.1.2)

- A new standard was added that requires occurrences outside of acceptance criteria must be evaluated. (D3.1.2)

Conditions for Storage

The following changes were made to the storage standards:

- If a warming event may have decreased the potency of a related CB unit, the unit must only be made available for administration as a nonconforming unit after approval of the CBB Medical Director and the transplant physician. (D6.5.2.3)
- A minimum of three (3) CB units per manufacturing method and storage conditions shall be assessed annually. (D6.6.1)
- CB units with the longest storage duration for each manufacturing method must be included in each annual assessment. (D6.6.1.1)
- Specifications for acceptance of stability results must be defined. (D6.6.2)
- The stability program must include requirements to assess additional CB units if a CB unit fails to meet specifications. (D6.6.2.1)

Testing

Cord blood unit testing

For related CB units, the results of positive microbial tests must include identity and sensitivities of the organism(s). In the sixth edition, the results were required to be reported to the prospective Clinical Program, but in the seventh edition they are required to be reported to the infant donor's mother and her physician, in accordance with Applicable Law and the CBB's policies and Standard Operating Procedures. (D9.3.2.2)

Maternal testing

A new standard was added to the Seventh Edition requiring CBBs to ensure samples are collected and stored for infectious disease testing. (D10.1.1)

Changes to Part E: Cord Blood Listing, Search, Selection, Reservation, Release, and Distribution Standards

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Policies and Standard Operation Procedures (SOPs)

Policies and SOPs for related and unrelated use were separated as applicable and new requirements were added.

The following policies and SOPs are required for unrelated use:

- Review of records. (E1.2.2.1)
- Qualification for listing and search of the CB units. (E1.2.2.2)
- Verification of HLA tying of the CB unit. (E1.2.2.3)

The following policies and SOPs are required for related use:

- Review of records. (E1.2.3.1)
- Continued storage and release. (E1.2.3.2)
- A process to prevent listing of related units for unrelated use. (E1.2.3.3)

The following policy and SOP is required for both:

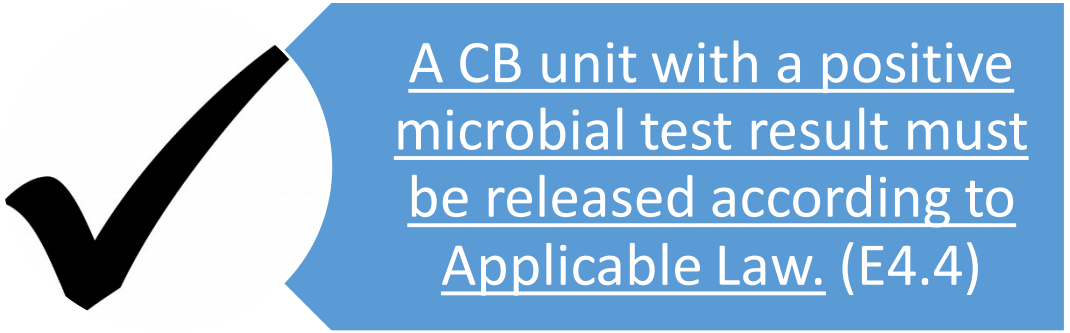
- A mechanism to ensure that CB units are released in accordance with Applicable Law and the agreement at the time of informed consent. (E1.2.4)

Review of CB Unit Records

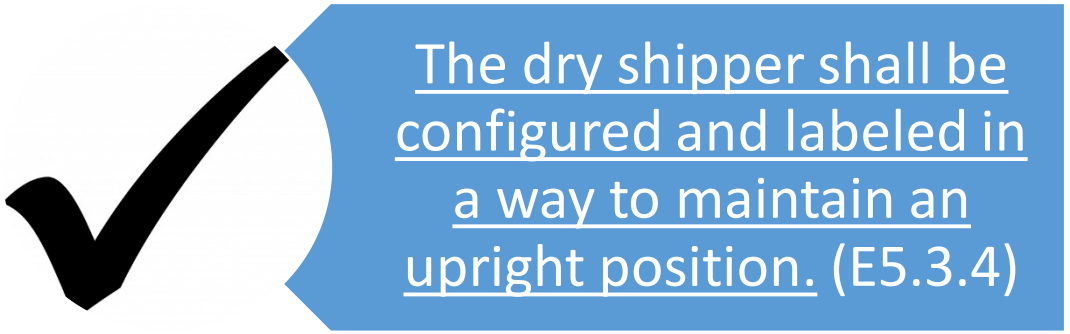
A new requirement was added for the CBB to have a policy and SOP for the comprehensive review of CB unit records, including eligibility determination, if required by Applicable Law. (E2.1.4)

CB Unit Distribution to a Clinical Program and Transportation and Shipping of Cryopreserved CB Units

Two new requirements were added:



A CB unit with a positive microbial test result must be released according to Applicable Law. (E4.4)



The dry shipper shall be configured and labeled in a way to maintain an upright position. (E5.3.4)

Clinical Outcome Data

A new requirement was added that the CBB must have a policy or Standard Operating Procedure to request information pertaining to a method for thawing and any further processing prior to administration within the recommended time period for every CB unit released for administration for hematopoietic reconstitution. (E7.1.2)

Become Familiar with the Standards

The following tools are available at http://www.factwebsite.org/cbstandards/:

- Standards and Accompanying Accreditation Manual
- Crosswalk from 6th to 7th edition and 7th to 6th edition.
- A redlined compare document highlighting edits from the 6th to 7th edition.
- Summary of Changes
- Cord Blood Self-Assessment Tool

Q&A

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Thank You

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