

# MEMORANDUM

**BLA 125594**  
**CMC Review of Original Submission**  
**HPC, Cord Blood**

**Cleveland Cord Blood Center**

**Division of Cellular and Gene Therapies**  
**Office of Cellular, Tissue, and Gene Therapies**

<b>Reviewed by:</b>	<b>Signature</b>
<b>Yong Fan, MD</b> Review Committee Chairperson	
<b>Fatima Abbasi, MS.</b>  (Flow Cytometry)	
<b>Joydeep Ghosh, Ph.D.</b> (Sterility testing and validation)	
<b>Safa Karandish, MT, ASCP</b> (Donor eligibility determination, collection , product labeling and tracking)	
<b>Concurred by:</b>	
<b>Steven Oh, Ph.D.</b> <b>Branch Chief</b>	

## Table of Contents

<b>EXECUTIVE SUMMARY .....</b>	<b>6</b>
<b>GENERAL INFORMATION .....</b>	<b>7</b>
<b>BACKGROUND/HISTORY .....</b>	<b>8</b>
<b>FACILITY DESCRIPTION AND FLOOR DIAGRAMS .....</b>	<b>8</b>
<b>HPC, CORD BLOOD DESCRIPTION .....</b>	<b>9</b>
<b>CONTAMINATION PRECAUTIONS.....</b>	<b>10</b>
<b>QUALITY PROGRAM.....</b>	<b>10</b>
<b>DONOR ELIGIBILITY DETERMINATION.....</b>	<b>10</b>
Donor Screening.....	10
Donor Testing.....	11
Final Donor Eligibility Determination .....	14
<b>CORD BLOOD COLLECTION .....</b>	<b>14</b>
Collection sites .....	14
Collection Procedure and Contamination Controls .....	17
Storage and Transportation of Collected Cord Blood Units .....	18
Collection Validation .....	20
<b>CORD BLOOD PROCESSING .....</b>	<b>21</b>
Overview .....	21
Reagents and Supplies .....	21
Criteria for accepting cord blood for further processing: .....	22
HPC, Cord Blood Processing:.....	22
In-Process Testing (Banking Criteria) .....	27
<b>PROCESS VALIDATION .....</b>	<b>27</b>
<b>CRYOPRESERVATION AND STORAGE.....</b>	<b>28</b>
Cryopreservation Procedure: .....	29
<b>FINAL LOT RELEASE TESTING .....</b>	<b>29</b>
<b>Safety Testing .....</b>	<b>30</b>
Donor Infectious Disease Testing .....	30
Hemoglobin (Hb) Testing for Homozygous Hemoglobinopathy .....	31
Sterility Testing.....	31
<b>Identity Testing .....</b>	<b>36</b>
ABO Blood Group and Rh Typing .....	36
HLA Typing (contract) .....	37

<b>Potency Testing .....</b>	<b>38</b>
Total Nucleated Cell (TNC) Counts: .....	39
(b) (4) .....	43
Enumeration of CD34+ Cells and TNC viability .....	44
<b>RELEASE TO INVENTORY, SHIPPING, AND PREPARATION INSTRUCTIONS.....</b>	<b>56</b>
Release from quarantine to permanent storage .....	56
Registry listing: .....	58
Cord blood Selection.....	58
Shipping to Transplant Center:.....	60
Shipping-dry shipper validation.....	60
Receipt and Storage Instructions: .....	60
Thawing and Emergency Recovery Instructions .....	60
Thawing and Cryoprotectant Removal Validation .....	61
<b>RETENTION SAMPLES.....</b>	<b>63</b>
<b>PRODUCT STABILITY AND EXPIRATION DATING: .....</b>	<b>64</b>
<b>CONTROL OF ASEPTIC PROCESSING .....</b>	<b>65</b>
<b>COMPUTER SYSTEMS AND VALIDATION.....</b>	<b>65</b>
<b>LABELING AND TRACKING.....</b>	<b>65</b>

Table 1: List of Testing Laboratories.....	7
Table 2: Donor Infectious Disease Tests .....	12
Table 3: Collection Sites.....	14
Table 4: Collection Supplies.....	17
Figure 1: Cord Blood Transport Containers .....	19
Table 5: Processing Reagents and Supplies.....	21
Figure 2: The (b) (4) device and disposable set .....	24
Figure 3: (b) (4) Processing Bag Set .....	24
Figure 4: Processing and Cryopreservation Flow Chart .....	25
Table 6: In-process Testing.....	27
Table 7: Post processing result .....	28
Table 8: Post thaw results .....	28
Table 9: Lot Release Acceptance Criteria for HPC, Cord Blood .....	29
Table 10: Sterility Test Method Suitability Data.....	34
Table 11: ABO/Rh Test results interpretation .....	37
Table 12: (b) (4) Manufacturer Stated Linearity.....	39
Table 13: Instrument (b) (4) .....	40
Table 14: Instrument (b) (4) .....	41
Table 15: Instrument (b) (4) .....	41
Table 16: Instrument (b) (4) .....	42
Table 17: Sample Carryover Results .....	42
Table 18: Correlation coefficient comparison between the .....	42
(b) (4) devices .....	42
Figure 5: Examples of (b) (4) colonies .....	43
Figure 6: Examples of (b) (4) colonies .....	44
Figure 7: Illustration of (b) (4) strategy for cord blood (b) (4) .....	46
Table 19: Example of Excel file results with data from analysis in CD34 from flow cytometer.....	47
Figure 8: Work flow diagram for validation process (b) (4) .....	48
Table 20: Flow Cytometry Reagents for Cord Blood Testing.....	49
Table 21: Flow Cytometry Validation Plan and Results .....	50
Table 23: Correlation Data (b) (4) .....	54
and (b) (4) .....	54
Table 24: External proficiency testing at CCBC .....	55
Figure 9: Release into Active Inventory Flow Chart.....	57
Figure 10: Listing and Distribution for Transplant Flow Chart.....	59
Table 25: Characteristics of the products thawed .....	61
Table 26: Post thaw data .....	62
Table 27: Post thaw TNC recovery.....	62
Table 28: Product integrity and final volume data.....	62
Table 29: Post-thaw results .....	63
Table 30: Age of the product for stability testing .....	64
Table 31: Preliminary Thaw results for HPC, Cord Blood from 2008, 2010 and 2012 .....	64
Table 32: Future stability study design.....	65
Figure 11: Example of Collection Barcode Label Sets.....	66
Figure 12: Partial label affixed to the cryopreserved HPC, Cord Blood .....	67

Figure 13: Package label and attachment to the canister .....	67
---	----

## EXECUTIVE SUMMARY

### Recommendation:

We recommend that BLA 125594 be approved. The approval should be granted only for the HPC, Cord Blood lots that will be manufactured after the approval date because the applicant did not demonstrate CGMP compliance until the date of approval.

### Product Overview

HPC, Cord Blood manufactured by The Abraham J. Phyllis Katz Cord Blood Foundation, dba Cleveland Cord Blood Center (CCBC) are minimally manipulated human cord blood cells. The applicant uses the automated (b) (4) system to reduce the plasma volume and the RBCs for the cord blood units (CBUs) collected at various collection sites. HPC, Cord Blood is cryopreserved in 10% DMSO containing 1% Dextran 40 using the controlled-rate freezer that is built-into the (b) (4) system and stored in the liquid nitrogen freezer unit of the (b) (4) system after satisfactory purity, identity, sterility and potency tests.

The shelf life of the HPC, Cord Blood under this BLA will be five (5) years after cryopreservation. This determination was made based on the stability data submitted by the applicant. The applicant plans an ongoing stability program to support the (b) (4) .

HPC, Cord Blood is shipped to the transplant centers frozen using validated and routinely re-qualified “Dry shippers” that are charged with liquid nitrogen to maintain the temperature at  $\leq -150^{\circ}\text{C}$  during shipping. The “Dry shippers” are equipped with temperature recorders to record and document the temperatures throughout shipping period.

The applicant will include thawing and washing instructions with the shipments and the methods have been fully validated.

In this review we use the terms “cord blood” or “cord blood units”, abbreviated “CBUs”, to refer to the collected cord blood prior to completion of processing. HPC, Cord Blood is the final product.

### Review Findings

The review team identified multiple deficiencies during review and inspection. All deficiencies were communicated to the applicant through letters, teleconferences, emails and during inspection. Examples of major deficiencies include inadequate raw material and certain manufacturing equipment qualifications, inappropriate donor eligibility determination procedure, deficient quality system and batch records. The applicant corrected all deficiencies and amended the application to the satisfaction of the review team. Based on the review of the information submitted in the original submission and nine (9) amendments, the review team has determined that the HPC, Cord Blood manufactured by the applicant now meets all the CGMP requirements and recommendations of the cord blood licensure guidance; therefore, the review team recommends approval of this BLA.

## GENERAL INFORMATION

The applicant, The Abraham J. Phyllis Katz Cord Blood Foundation, dba Cleveland Cord Blood Center (CCBC) is a non-profit organization that collects, processes, stores and distributes minimally manipulated unrelated umbilical cord blood products for clinical applications (please see the intended use below).

CCBC is accredited by the American Association of Blood Banks (AABB), The Foundation for the Accreditation of Cellular Therapy (FACT), and is designated as a Health Resources and Service Administration (HRSA) funded center. CCBC is a member bank of the National Marrow Donor Program (NMDP). The CCBC is located at:

25001 Emery Road, Suite 150  
Warrensville Heights, Ohio 44128  
216-896-0360  
FEI# 3006718574

CCBC has four (4) collection sites, performs manufacturing (other than collection) and most of the product testing at the main facility. The HLA typing and donor infectious disease testing are performed by contract laboratories. Detailed testing laboratory information is provided in the table below:

**Table 1: List of Testing Laboratories**

Lab name and location	Tests performed	Certificates/Accredits
CCBC	Total nucleated cells count	CLIA, FACT
	CD34+ cell enumeration and viability determination	
	(b) (4)	
(b) (4)	HLA typing	(b) (4)
(b) (4)	HLA typing	(b) (4)
CCBC	Hemoglobinopathy test	CAP and CLIA
CCBC	ABO Rh blood type	AABB and CAP

(b) (4)	Infectious disease testing	(b) (4)
CCBC	Sterility testing	CLIA, CAP

### **INTENDED USE:**

HPC (hematopoietic progenitor cells), Cord Blood is an allogeneic cord blood hematopoietic progenitor cell therapy indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.

The risk benefit assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.

### **BACKGROUND/HISTORY**

The Abraham J. Phyllis Katz Cord Blood Foundation, dba Cleveland Cord Blood Center (CCBC) is the manufacturer of HPC, Cord Blood under this license application.

This organization was established in 2007. Since then, the applicant has collected over (b) (4) cord blood units (CBUs) and banked over (b) (4) frozen units and distributed more than (b) (4) HPC, Cord Blood products under IND7555 that is sponsored by the National Marrow Donor Program (NMDP) to transplant centers in the United States and 15 other countries. The applicant is seeking licensure of the HPC, Cord Blood units that are manufactured using the (b) (4) method. Inventory that does not meet licensure requirements will be distributed under IND(s).

### **FACILITY DESCRIPTION AND FLOOR DIAGRAMS**

The main facility consists of (b) (4) space with (b) (4) workflow. It includes designated areas committed to CBU receipt and accessioning, processing, cryopreservation and sampling for QC and release testing. The processing area includes a laboratory space with HEPA-filtered air (non-classified) and a clean room suite consisting of a Class (b) (4) Clean Room and an adjacent Class (b) (4) Gowning Room. Access to the processing facility is restricted via (b) (4) locking doors and is limited to processing facility personnel during processing periods. All manufacturing procedures except donor screening and testing, collection and HLA testing are performed at this facility.

The applicant submitted the facility floor plans (diagrams) for this facility and these can be located in the establishment portion of the CMC section of the original BLA submission.



## HPC, Cord Blood DESCRIPTION

HPC, Cord Blood manufactured by The Abraham J. Phyllis Katz Cord Blood Foundation, dba Cleveland Cord Blood Center (CCBC) is a minimally manipulated allogeneic unrelated cord blood hematopoietic progenitor cell therapy product.

The applicant has contracts with two hospitals in Cleveland area and two hospitals in Atlanta Georgia for collection of cord blood.

Cord blood collection is performed in-utero before the delivery of the placenta in the hospital's labor and delivery area. After collection, the bag is transported at controlled room temperature (15-25°C) to the bank for processing and cryopreservation.

Processing is performed using an (b) (4) cord blood processing system with (b) (4) to partially remove red blood cells (RBCs) and plasma. (b) (4) samples are taken for in process and final lot release testing including TNC, Viability, CD34%, (b) (4), ABO/Rh, HLA and sterility. Retention samples including plasma, RBCs and nucleated cells are taken after processing, before cryopreservation.

The processed HPC, Cord Blood is cryopreserved in 10% DMSO containing 1% Dextran 40 and stored using the (b) (4) controlled rate freezing and storage system in quarantine. The HPC, Cord Blood is listed in a searchable database after all release criteria are met so that the transplant centers and transplant registries can match the HPC, Cord Blood with patients who need transplants.

**The UNII codes, NDC code, and name of the product are listed below.**

**Proprietary Name:** The proposed proprietary name, (b) (4) is determined to be unacceptable by Dr. Loan Nguyen (please see her review in EDR for more details). The applicant then proposed Clevecord, which was found to be acceptable.

**Non-proprietary Name:** HPC, Cord Blood

**Active Ingredient:**

CORD BLOOD HEMATOPOIETIC PROGENITOR CELLS

**UNII Code:** (b) (4)

**Inactive Ingredients:**

DEXTRAN 40

DIMETHYL SULFOXIDE (DMSO)

(b) (4)

Citrate Phosphate Dextrose (CPD)

**UNII Code:**

(b) (4)

(b) (4)

(b) (4)

**Therapeutic or Pharmacologic Class:** allogeneic cord blood hematopoietic progenitor cells therapy

**Dosage Form:** Injectable Suspension

**NDC #:** The applicant requested an NDC code exemption because the applicant uses the ISBT 128

The ISBT 128 facility code: (b) (4)

The ISBT 128 product code: (b) (4)

## **CONTAMINATION PRECAUTIONS**

Please also see CGMP review by Division of Manufacturing and Product Quality, OCBQ.

### **In-process controls**

- 1) Raw materials used in manufacturing are pre-qualified;
- 2) The product is manufactured using a FDA cleared functionally closed system,
- 3) Processing takes place in a class (b) (4) with appropriate environmental monitoring;
- 4) Disinfecting the working area before and after each processing and sampling;
- 5) Process one unit at a time;
- 6) Use sterile disposables;
- 7) Operators change gloves between procedures;
- 8) Disinfect (b) (4) each procedure;
- 9) Cryopreservation and storage in a sealed overwrap;
- 10) Labeling controls including printing and witness checking for all labels;
- 11) Validated sterility testing for each unit to ensure no contaminations;
- 12) Manufacturing staff are trained for aseptic processing techniques.

## **QUALITY PROGRAM**

(Please also see CGMP review by Division of Manufacturing and Product Quality, OCBQ)

The applicant did not provide information regarding the Quality System. This section is reviewed by Division of Manufacturing and Product Quality, OCBQ and is also assessed during pre-licensure inspection.

## **DONOR ELIGIBILITY DETERMINATION**

CCBC's donor eligibility determination procedures include screening and testing of the cord blood donors for risks of relevant communicable diseases or disease agents (RCDADs).

### **Donor Screening**

CCBC's donor screening includes: 1) medical history interview of the birth mother, and 2) review of the maternal and infant donor's medical records looking for clinical and physical evidence of RCDADs (SOP-H0012). Trained collection coordinators interview the birth mother according to SOP-H0012. The medical history interview is completed within 14 days of cord blood unit collection and when necessary, a phone interview may be performed. The collection coordinators also review the birth mother's medical records including the admission data, labor and delivery information, the infant's condition at birth and during the hospital course. The UCB Collection and Maternal/Infant Data (Form H-0012a) is utilized to obtain and document the

required information about the maternal and family medical history and any identified RCDAD risk factors.

If any of the following conditions or complications is present, the unit will not be accepted for banking (UCB Collection and Maternal/Infant Data Form H0012 Mother's Admission Data Action Guide):

- Positive pre-natal maternal blood test results (HBsAg, HIV, Syphilis, HCV, Zika virus)
- Rupture membrane before delivery, malodorous placenta or amniotic fluid/diagnosis of chorioamnionitis
- Physical evidence of sexually transmitted diseases such as genital ulcerative disease, herpes simplex, syphilis, chancroid and other relevant communicable diseases.
- Evidence of congenital infection, sepsis, malformation including absent digits on hands or feet, absent radii, extra digits, horseshoe kidney, dwarfism, albinism, microcephaly, hemi-hypertrophy, more than 6 café-au-lait spots.

Donors are screened for risk factors associated with HIV 1 and 2, HBV, HCV, Syphilis, HTLV I and II, WNV, Sepsis, Vaccinia, TSE (CJD/vCJD), and xenotransplantation and Zika virus. In addition, donors are screened for (b) (4) and other blood borne parasitic diseases (b) (4) which are not currently required by the FDA.

***Reviewer comment:***

*In the initial application, CCBC didn't include the medical history questionnaire and the associated decision or action guides. This information was requested in the filing letter dated 8/7/15. Additionally, on 3/11/16, CCBC was reminded that the recommendations regarding screening HCT/P donors for Zika virus should be implemented by March 29, 2016. The revised version of the donor screening procedure and forms (SOP-H0012, UCB Collection and Maternal/Infant Data Form H0012 Mother's Admission Data Action Guide), which include donor screening for Zika virus, were submitted in Amendment 6. In SOP-H0012, the instructions related to the timeframe for sexual contact with a man who has had Zika virus risk factors are not stated correctly (step 6.123). The timeframe listed on the medical history questionnaire and the Cord Blood Maternal Risk Action Guide is correct. The applicant submitted revised SOP-H0012 in Amendment 11.*

## **Donor Testing**

The infectious disease tests are performed by (b) (4)

***Reviewer comment:***

*In the initial application, CCBC provided (b) (4) Blood Registration number (b) (4) instead of the HCT/P registration (b) (4) CCBC submitted (b) (4) HCT/P Registration information in Amendment 6 (CMC, Sect. 31.4A, Rev. 2.0).*

Maternal blood specimens for donor testing are obtained by the hospital staff following the CCBC's instructions (SOP-H0013). The specimens are collected within 7 days of the infant's delivery. Before collection of the specimens, the birth mother's information (name, hospital #, DOB) on the hospital wristband and on the hospital generated labels are verified and the mother is asked to verbally verify her name. The blood collection tubes are labeled at bedside with hospital generated labels and the ISBT 128 barcode labels (see Labeling and Tracking section). The collection date, time, and the staff identification are documented on the UCB Collection and Maternal/Infant Data Form H0012a). Information regarding transfusion of blood products and/or infusion of intravenous fluids is also documented on this form. Maternal blood specimens are not accepted for testing if the birth mother has received a transfusion of more than [REDACTED] of blood, blood components within [REDACTED] or more than [REDACTED] of crystalloids within [REDACTED] before the specimens for infectious disease testing are collected (SOP-L0084 and UCB Collection and Maternal/Infant Data Form H0012a Page 1 Action Guide). Maternal specimens are transported with the collected units to CCBC and subsequently shipped to [REDACTED] for testing in accordance with SOP-L0025 (Infectious Disease Testing: Maternal Sample Handling and Shipping Instructions).

***Reviewer comment:***

***The SOP and forms submitted in the initial application did not include documentation of crystalloid infusion. The revised SOP-L0084, UCB Collection and Maternal/Infant Data Form H0012a and the corresponding Action Guide were submitted in Amendment 6). The described procedure is acceptable.***

Birth mothers are tested for the following:

*FDA required tests:* Anti-HIV 1 and 2, HIV-1/HCV NAT, Anti-HTLVI and II, HBsAg, Anti-HBc, Anti-HCV, Syphilis, Anti-CMV

*Additional tests not currently required by the FDA:* WNV NAT, HBV NAT, Anti- *T. cruzi*.

The testing laboratory performs the tests using FDA-licensed, approved or cleared donor screening tests (Revised SOP-L0084 and CMC, Sect. 31.4A, Rev. 2.0 were submitted in Amendment 6).

**Table 2: Donor Infectious Disease Tests**

Test	Assay Name	Manufacturer
Hepatitis B surface Antigen (HBsAg)	(b) (4)	(b) (4)
Hepatitis B core Antibody (HBc)	(b) (4)	(b) (4)
Anti-Hepatitis C (HCV)	(b) (4)	(b) (4)
Anti- Human T-Lymphotropic Virus (HTLV)	(b) (4)	(b) (4)
Anti- Human Immunodeficiency	(b) (4)	(b) (4)

Virus 1 and 2 (HIV)	(b) (4)	
HIV-1/HCV/HBV Nucleic Acid Test	(b) (4)	(b) (4)
<i>Treponema pallidum</i> (Syphilis)	(b) (4)	(b) (4)
Cytomegalovirus (CMV) Antibody	(b) (4)	(b) (4)
West Nile Virus (WNV) Nucleic Acid Test	(b) (4)	(b) (4)
<i>Trypanosoma cruzi</i> (b) (4)	(b) (4)	(b) (4)

CCBC defers donors who test positive or reactive for the above donor screening tests, except for CMV and Hepatitis B core antibody. CCBC determines donors who test reactive for Hepatitis B core antibody as ineligible and units from such donors may be used under an IND if there is a documented urgent medical need. CMV results are reported to the transplant center. (Amendment 6: SOP L-0084, Maternal/Cord Blood Unit Infectious Disease Marker Action Guide).

For birth mother notification and counselling purposes, CCBC performs confirmatory tests for positive infectious disease test results (except for CMV). CCBC's medical director or designee notifies the birth mother's physician if confirmatory test results are positive and the notification is documented in the unit batch record (Amendment 6: SOP L-0084).

***Reviewer comment:***

*In the filing letter dated 8/7/15, the applicant was asked to clarify whether a treponemal or non-treponemal screening test is used for syphilis. In the response letter (email received on 11/23/15 and submitted in Amendment 3), the applicant explained that a treponemal donor screening test (b) (4) is used, and if the initial results are reactive, another treponemal test (b) (4) is used as a confirmatory assay. If the results with (b) (4) are negative, the donor is determined ineligible and the unit may be used under the IND. The applicant was informed that if the initial treponemal test is reactive, the donor must be determined ineligible and the additional testing with another treponemal test could not serve the role of a "confirmatory" test. The revised SOP-L0084 and the Maternal/Cord Blood Unit Infectious Disease Marker Action Guide submitted in Amendment 6, still states that that a (b) (4). The applicant was again reminded that the additional testing could not be considered as a (b) (4). Additionally, in section C of SOP-L0084, the applicant notes that donors with positive screening test for syphilis are deferred regardless of confirmatory testing results; however, according to the Action Guide the donor is considered ineligible and not deferred. The applicant submitted the revised SOP-L0084, which now states that the (b) (4) (Amendment 11).*

## Final Donor Eligibility Determination

Cord blood units are maintained in quarantine until the donor eligibility determination is completed. CCBC determines the donor to be eligible if the donor screening does not identify any risk factors for RCDADs and all the infectious disease test results are negative or non-reactive, except for CMV (CMV results are reported).

CCBC Hospital Liaisons (licensed RN or NP) or the medical director is responsible for reviewing all the screening and testing results and making the final donor eligibility (DE) determination. Hospital Liaisons will contact the donor if additional information or confirmation is needed. The DE determination is documented on the HPC, Cord Blood Release to Inventory Form (WKS-L0028a). Additionally, before HPC, Cord Blood units are distributed to the transplant center, the medical director reviews the donor screening and testing information and records the final DE determination in NMDP's (b) (4) system. The summary of records which include the list of infectious disease test results (HPC, Cord Blood Unit Report and the Infectious Disease Marker Report for HPC, Cord Blood) and the Final Declaration of Eligibility form accompany the unit (SOPs L0028, L0083, L0066).

CCBC maintains units from certain ineligible donors (reactive test results for Hepatitis B core antibody or risk factors based on the travel history) in the searchable inventory; however, units from donors for whom the DE determination is not completed or from ineligible donors are not licensed but may be released under an IND (SOP-L0028, Cord Blood Maternal Risk Questionnaire Action Guide and Maternal/Cord Blood Unit Infectious Disease Marker Action Guide).

### *Reviewer comment:*

*According to the procedure submitted in the initial application, the medical director or qualified designee did not document the final DE determination based on the review of all the screening and testing results before the units were released to the searchable inventory. The revised SOP-L0028 and (b) (4) were submitted in Amendment 6. CCBC's revised DE determination procedure is acceptable.*

## CORD BLOOD COLLECTION

Cleveland Cord Blood Center (CCBC) currently collects cord blood units at total of 4 hospitals (2 in Ohio and 2 in Georgia). Cord blood is collected by trained healthcare providers in both vaginal and C-section deliveries, following the CCBC in-utero collection procedure (SOP-H0008).

### Collection sites

The following is the current list of collection sites:

**Table 3: Collection Sites**

	Collection Hospital	Address
1	Cleveland Clinic Foundation Hillcrest Hospital	6780 Mayfield Rd, Mayfield Heights, OH 44124

2	Cleveland Clinic Foundation Fairview Hospital	18101 Lorain Ave, Cleveland, OH 44111
3	Emory University Hospital Midtown	550 Peachtree Street, NE, Atlanta, GA 30308
4	Piedmont Hospital	1968 Peachtree Road, NW, Atlanta, GA 30309

### Collection Site Qualification

CCBC collection site qualification includes the following elements (Cleveland Cord Blood Center Collection Site Qualification Process, Amendment 6):

- Service agreement
- Training program agreement
- Adequate space to facilitate cord blood collection, and storage of supplies and units prior to shipment to CCBC
- Adequate support for review and approval of consent forms, collection of maternal/infant history and delivery information, and collection of maternal specimens

As part of the agreement, CCBC trains the designated hospital staff (Cord Blood Collection Coordinators and Collectors) responsible for collection related activities (see section below). Cord Blood Collection Coordinators and Collectors (physicians or midwives) are required to complete CCBC's training and competency program, and comply with CCBC's policies and procedures. Each hospital is required to provide a general administrative area and a secured storage space for supplies and the collected units. Participating hospitals are also required to review and approve the maternal consent forms.

#### *Reviewer comment:*

*The collection site qualification process is acceptable.*

### Collection Site Staff Training

CCBC Hospital liaisons (licensed RN or NP) are responsible for coordinating the collection activities and training of the designated trainers and collection coordinators at the hospitals. The training program includes procedures related to consenting the birth mothers, medical history interview, collection kit assembly, collection of cord blood and maternal specimens, labeling, storage and transportation of collected units from the hospital to CCBC processing laboratory. All collection personnel at the hospitals are required to review the relevant SOPs and complete a 3-phase training program: 1) observation, 2) performance of the procedure, and 3) demonstration of proficiency. The (b) (4) competency include review of the SOPs, completion of a quiz (acceptance score (b) (4) and performance of the procedures under direct observation. Additionally, all CCBC collection site personnel must review the online training module provided by the National Marrow Donor Program and complete an online test (acceptance score (b) (4)). Personnel are retrained and must retake the tests when necessary. Healthcare providers (e.g. physicians, midwives) who collect the cord blood units are required to read the relevant SOPs, attend on-site training and education programs, and complete the online training module provided by the National Marrow Donor Program and achieve a score of (b) (4) on the online test (SOP-H0021 Training at Collection Sites).

#### *Reviewer comment:*

*In the filing letter dated 8/7/15, CCBC was asked to submit the training procedure for collection staff. SOP-H0021 Training at Collections Sites was submitted in Amendment 3. The training procedure is acceptable.*

### **Donor Recruitment, Pre-screening and Consent**

Trained Collection Coordinators at hospitals are responsible for pre-screening the potential donors and obtaining consent from the birth mothers (SOP-H0032 and SOP-H0009). The informed consent is obtained when the birth mother is fully alert and not under distress. The birth mother's admission records are reviewed to determine if she meets the initial qualification criteria for cord blood donation.

The following are the exclusion criteria:

- $\leq 34$  weeks gestation
- $< 18$  years of age
- Multiple births
- Infant known or found to have a genetic disease that affect the hematopoietic systems, including diseases associated with a high risk of leukemia such as Down's Syndrome
- Positive results for HIV or HBV, or known to have CJD
- No prenatal care
- Infant known to have 2-vessel cord

Mothers must sign a consent form prior to collection of cord blood. Consent forms are collection site specific and are approved by each collection hospital. Consent will not be obtained if the mother is uncomfortable, under distress or not fully alert. The consent form is stamped with "NOT FOR RESEARCH" if the birth mother does not consent to using her baby's cord blood for research purposes in case the collected unit does not meet the banking criteria. Such units are discarded.

### **Collection Supplies**

Collection supplies are visually inspected for defects, damage and expiration date (SOP-H0030). Collection kits which include the necessary supplies for cord blood collection are assembled and stored in the designated, key-lock protected storage areas at the hospitals. The storage area temperature is monitored using a min/max thermometer and the temperature range is documented on (b) (4) basis (acceptable range 14.5-25C°). Any temperature excursion is reported to the CCBC processing laboratory for investigation.

Each collection kit consists of Pall Medical Cord Blood Collection Bag containing 35 mL of CPD (manufacturer ID#: 791-08, 250ml capacity), (b) (4) -Iodine Swab stick, (b) (4) for collection of maternal samples, pre-printed ISBT barcode labels for the collection bag and the maternal specimen tubes, biohazard transport bags, and related forms/documentation for collection. At time of collection, the lot# and expiration date of supplies are documented on worksheets which are maintained in the batch for the collected unit. The following table includes the list of supplies and the qualification procedure.



**Table 4: Collection Supplies**

Supplies	Vendor/Manufacturer	Grade / Regulatory Status	Qualification Procedure	COA
Cord blood collection bag	Manufactured by (b) (4) for Pall Corp.	FDA NDA approved and CE marked under the Medical Devices Directive for the collection of cord blood.	Visual inspection	Yes
(b) (4) Iodine swabs used in cord blood collection	(b) (4)	GMP	Visual inspection	Yes
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Specimen Bag Size: 5"x9" (Small)	(b) (4)	Compliance: FDA		
(b) (4) Biohazard Specimen Transport Bags Size: 12"x15" (Large)	(b) (4)	Certifications/ Compliance: OSHA, NCCLS	Visual inspection	
(b) (4)	(b) (4)		(b) (4)	

**Reviewer comment:**

***Pall Medical Cord Blood Collection Bag 791-08 has NDA approval (BN800222). Other supplies listed in the table above do not come in direct contact with the collected product. The above table was submitted in Amendment 3.***

## Collection Procedure and Contamination Controls

CCBC has established the following controls for the collection procedure (SOP-H0008):

1. Cord blood is collected in both vaginal and C-section deliveries, before the placenta is delivered (*in-utero* collection).

2. Collection coordinators are responsible for preparing all the paperwork, labeling and packaging the collected units as well as verifying that the healthcare providers (e.g. physician, midwife) collecting the units have documented training.
3. The birth mother's name and identification number on the hospital wristband is verified against the information on the hospital generated maternal labels and the mother is asked to state her name for additional verification.
4. To minimize risk of contamination, cross contamination or mix-up:
  - collection and preparation of the associated documentation are handled one at a time. Lot# and expiration date of supplies are documented on the UCB Collection and Maternal/Infant Data Form (H0012a).
  - single use, sterile collection bag and supplies are used for collection.
  - venipuncture site on the cord is disinfected with (b) (4) -Iodine swabstick.
  - cord blood is collected into the collection bag by gravity flow and mixed with the anticoagulant in the bag during collection.
  - after completion of collection, the needle safety cover is pulled into the locked position and the clamp on tubing is closed.
  - collection bag is labeled with the hospital generated maternal label and the Donation Identification Number barcode label (see Labeling and Tracking section for details), and placed inside a pre-labeled ziplock bag.
  - Date and time of collection and other relevant information on the birth mother and the newborn are documented on the UCB Collection and Maternal/Infant Data Form (H0012a).
  - A hospital generated maternal label and the Donation Identification Number barcode label (see Labeling and Tracking section for details) are placed on the last page of Form H0012a.

***Reviewer comment:***

***The collection procedure and the established controls are acceptable.***

## **Storage and Transportation of Collected Cord Blood Units**

The ziplock bag containing the collected cord blood unit is placed in an insulated transport container that contains two room temperature gel packs and a temperature data-logger. The maternal specimens that are in a separate ziplock bag and the relevant documentation and forms are placed in the same container. The transport box is temporarily stored in a designated locked area at the delivery hospital until pick-up by the courier (SOP-H0016).

**Figure 1: Cord Blood Transport Containers**



The cord blood units collected at hospitals in Cleveland are transported by designated local couriers or CCBC staff and the chain of custody is documented on a transport log.

***Reviewer comment:***

*SOP-H0016 in the original submission did not describe how units collected at hospitals in Georgia are transported to CCBC. The revised SOP submitted in Amendment 6, explains that for collection sites in Georgia, the transport containers are shipped via air using a medical courier company, and the status of each shipped can be tracked using the company's website.*

At the CCBC processing laboratory, each transport container is inspected and opened one at a time. The temperature data logger is removed and the data is downloaded using the (b) (4) . The acceptable temperature is 15-25°C. The temperature graph is reviewed and any excursions are documented and reported to the Quality Unit.

***Reviewer comment:***

*Shipping container validation reviewed by DMPQ. Cord blood units that are not transported within the acceptable temperature range are either discarded or used for non-clinical research.*

**Initial Cord Blood Qualification Criteria**

Upon receipt, the cord blood unit and the maternal specimens are visually inspected; labels and the associated documentation are reviewed and verified for accuracy and completeness. Before weighing the collected unit, the collection bag tubing is heat sealed and the needle is detached.

The following pre-processing acceptance criteria must be met (SOPs- L0082, L0088 and L0098):

- Cord blood unit collected by a collector with documented training
- Donor identification information (hospital generated maternal labels and the assigned DIN) on the unit container and maternal specimens match all the associated documentation including the signed consent form
- Pre-processing cord blood unit weight: (b) (4)
- Sufficient time to cryopreserve the unit within 48 hours of collection

Additionally, the cord blood unit is not accepted for processing if any of the following is documented by the hospital collection staff:

- suspected chorioamnionitis at time of delivery
- cord not cleaned with (b) (4) -Iodine swabstick before collection
- fetal malformation including metabolic disorders

- chromosomal or structural abnormalities
- umbilical cord with 2 vessels

***Reviewer comment:***

***The pre-processing qualification criteria are acceptable. Units that are not accepted for processing are either discarded or used for research.***

## **Collection Validation**

The collection procedure was validated in the first year that CCBC started their operation (Protocol VAL-0033: Qualification of CBU Collections -2008/2009 study). In this prospective study, total of (b) (4) randomly selected cord blood units that were collected by trained staff at Hillcrest Hospital in Cleveland were evaluated. The following were the pre-defined acceptance criteria:

(b) (4)

(b) (4)

For one unit, the timeframe to processing could not be calculated because the collection time could not be confirmed.

***Reviewer comment:***

***This validation is acceptable considering that CCBC discards or uses the unit for research if the predefined timeframe for cryopreservation or other pre-processing acceptance criteria are not met.***

In 2015, CCBC performed another prospective study (Protocol VAL-0013: Qualification of CBU Collections) evaluating the performance at each collection site. Cord blood units collected at the 4 collection hospitals (Ohio hospitals: Hillcrest, Fairview; Georgia hospitals: Emory, Piedmont) were evaluated in this study. From each collection hospital, (b) (4) randomly selected per (b) (4) units evaluated). The following expected results were set based on the historical experience:

-

(b) (4)

(b) (4)

*This study provides additional information regarding the overall performance at each collection site. CCBC provides retraining for collectors on as needed basis. Additionally, any unit that does not meet the pre-processing acceptance criteria or is contaminated is discarded or used for research.*

## Overview

## Reagents and Supplies

Supplies	Vendor	Grade	COA/PI
Human serum Albumin	(b) (4)	Clinical	Yes
10% Dextran 40	(b) (4)	FDA approved for IV infusion	Yes
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)

bag set	(b) (4)	(b) (4)	
(b) (4) MSO, 5%Dextran 40 in WFI)	(b) (4)	(b) (4)	Yes
Syringes and needles	(b) (4)	(b) (4)	NA
Transfer packs	(b) (4)	510k cleared	Yes
(b) (4) vials	(b) (4)	(b) (4)	NA
Needles	(b) (4)	(b) (4)	NA
Test Tubes	(b) (4)	(b) (4)	NA
Sterile Tubing Welder	(b) (4)		NA
Plasma transfer set	(b) (4)	510k cleared	Yes
Overwrap	(b) (4)	510k cleared	Yes

#### Accessioning:

The CCBC staff receives transport box and download data logger, confirms the Cord Blood Unit (CBU), maternal sample, and consent forms have been received, records the CBU receipt date and time and accessioning information on worksheet (WKS-L0082a). The accessioning staff also places a barcode and record receipt date and time on the Cord Blood Accession Log (WKS-L0037b).

#### Criteria for accepting cord blood for further processing:

1. The shipping package and the collected unit(s) pass the visual inspection (no damage or clot) and labels are verified.
2. The temperature maintained between 15 to 25°C during storage and transportation.
3. The collected CBU should not be less than (b) (4).
4. The birth date and collection time is verified to ensure that the processed CBU is cryopreserved within 48h of collection.
5. Minimum total nucleated cell count (TNC)  $1.25 \times 10^9$ .

#### HPC, Cord Blood Processing:

Closed collection bag and processing systems are used that avoid exposure of cord blood to the open atmosphere. All processing materials and solutions are purchased as ready-made pre-sterilized, single-use units from selected vendors. Specific procedures requiring entry or exit into the bag set are performed inside a (b) (4)

(1). (b) (4)  
A single (b) (4) is aseptically removed from each CBU for (b) (4) testing (TNC, ABO, Hemoglobin and HLA tests).

(2). (b) (4)

6 pages have been determined to be not releasable: (b)(4)

(b) (4)

### **Cryopreservation Procedure:**

**Qualification of the cryoprotectant,**(b) (4) :

(b) (4)

(b) (4)

**Qualification of the** (b) (4)

The (b) (4) qualification is evaluated and documented by Chad Burger, the DMPQ reviewer.

### **Quarantine:**

After controlled-rate freezing, each CBU remains in the same (b) (4) under quarantine until all the required release testing is completed and results accepted. The final product is then released to the searchable inventory.

## **FINAL LOT RELEASE TESTING**

Listed below in Table 9 is a summary of the lot release tests that are performed on each HPC, Cord Blood lot, the acceptance criteria, and test methods used. Infectious disease testing is performed on a maternal blood sample, hemoglobin analysis and ABO/Rh typing are done using (b) (4) cord blood samples, and the rest of the testing is done on (b) (4) HPC, Cord Blood samples.

**Table 9: Lot Release Acceptance Criteria for HPC, Cord Blood**

<b>Product Characteristics</b>	<b>Testing/ inspecting</b>	<b>Criterion</b>	<b>Test Method</b>
<b>Safety</b>	Infectious disease- 21 CFR1271.45-90	All tests negative except for non-treponemal test for syphilis when confirmatory test is negative and CMV results which are recorded.	Performed by (b) (4) Testing Laboratory using FDA licensed or approved test kits



		<i>Performed on maternal blood sample within 7 days of birth [21 CFR 1271.80 (a)(b)].</i>	
	Sterility-Bacterial/fungal cultures	No Growth	Performed by the applicant using the (b) (4)
	Hemoglobin	No homozygous hemoglobinopathy	Performed by the applicant using (b) (4)
<b>Integrity</b>	Container, closures, seals	Intact	Visual cord blood bag inspection
<b>Purity and Potency</b>	Total nucleated cells (TNC)	(b) (4)	Performed by the applicant using the (b) (4)
	Viability of TNC	> 85%	Performed by the applicant using (b) (4)
	Viable CD34 <sup>+</sup> cell count	$\geq 1.25 \times 10^6$	Performed by the applicant using flow cytometry
	(b) (4)	(b) (4)	(b) (4)
<b>Identity</b>	HLA typing	Recipient and Donor match level reported	(b) (4)
	ABO and Rh	Recipient and Donor match level reported	Performed by the applicant using FDA cleared test kits

## Safety Testing

### Donor Infectious Disease Testing

(Please see Donor Eligibility section)

## Hemoglobin (Hb) Testing for Homozygous Hemoglobinopathy

### Description:

The applicant uses The (b) (4) (that uses (b) (4) to screen a (b) (4) sample aliquot of each CBU for the presence of abnormal hemoglobin. This system is an FDA cleared medical device for detecting hemoglobinopathy (b) (4). The system consists of a (b) (4)

#### Detection of (b) (4)

CBUs are disqualified if positive for both Hb S and Hb C, or for any homozygous hemoglobinopathy.

The applicant participates in the College of American Pathology (CAP) Hemoglobinopathy Proficiency Program using the (b) (4). The proficiency samples are treated the same way as the cord blood sample. The trained processing facility staff members are assigned a test event on a random rotation to ensure competency. Results obtained from (b) (4) different test samples are evaluated and compared to approximately (b) (4) other laboratories (b) (4) a year.

### Qualification of (b) (4) Testing System for Performing (b) (4) y Screen

The applicant performed a study to compare the (b) (4) testing system (a quantitative method) and the existing qualitative method of (b) (4). A total of (b) (4) samples were analyzed using both systems, (b) (4) of these are normal and (b) (4) of these are abnormal on both systems.

### Reviewer's comment:

*The applicant compared a 510(k) cleared medical device, (b) (4) with another instrument (b) (4) which is also a 510(k) cleared device. The data submitted with this comparison study has demonstrated that the (b) (4) device functions as intended.*

## Sterility Testing

### Proposed Sterility Test Procedure and Lot-release Specification

The Cleveland Cord Blood Center has proposed to perform the Sterility Test (for lot release) for their HPC, Cord Blood using the following instrument, media and conditions:

1. (b) (4)

2. (b) (4)

3. (b) (4)

4. (b) (4)

5. (b) (4)

6. (b) (4)

**Reviewer Comments:**

1. The (b) (4) system is a widely-used (b) (4) and has been used for the Sterility test of other products reviewed by this office. The composition of the (b) (4) is available on the (b) (4) website and the information is adequate.
2. The proposed (b) (4) sample (per media bottle) is a process by-product consisting of (b) (4). The applicant is proposing (b) (4) HPC, Cord Blood product volume is very (b) (4) and all of it is needed for a successful transplant in the recipient.

*Based on the above facts and the*

- closed nature of the processing method,
- total volume of the by-product RBC and plasma fractions (b) (4)
- same time of origin for product and by-product fractions, and
- results of the method suitability (bacteriostasis/fungistasis) testing (described below),

*we agree that the proposed test sample is an appropriate alternative to use for the Sterility Test of HPC, Cord Blood manufactured by the Cleveland Cord Blood Center.*

3. The applicant has stated (reference: original submission) that (b) (4) reference laboratory for identification of the contaminant. Regular preventive maintenance is performed on the (b) (4) instrument by the manufacturer, and temperature verification is recorded (b) (4) by the CCBC Processing Facility staff – this is acceptable.

**Method Validation:**

The applicant is using an alternative qualitative method for the Sterility Test and has cross-referenced the (b) (4) for the validation of specificity, limit of detection, ruggedness and robustness of the (b) (4) system – reference: email communication dated November 23, 2015 from STN 125594/0/3.

**Reviewer Comments:**

1. Based on our prior experience (data from published scientific literature and previous HPC, Cord Blood BLAs submitted to this office) and a survey of the data submitted by (b) (4) we agree that this system ((b) (4) combination has adequate levels of specificity (able to detect a very broad range of microorganisms), limits of detection (able to detect (b) (4) ruggedness (for example, similar degree of precision of test results obtained by different analysts and from different media lots) and robustness

*(for example, the system remain unaffected by deliberate variation of ambient temperature). However, it should be noted that the above validation studies were done in the presence of a different matrix (for example, (b) (4) and therefore, we considered the (b) (4) just as an (b) (4) detection method (and not as a (b) (4) Method) in this case.*

- 2. The applicant has confirmed that the IQ/OQ verification for their (b) (4) instruments was executed by the manufacturer (b) (4) and the instruments use the (b) (4) (reference: email communication dated November 23, 2015 from STN 125594/0/3) – we agree that the instruments are appropriately qualified; the (b) (4) is cleared by CDRH.*
- 3. The method suitability data (described below) provided additional assurance on the compatibility of the test method.*

**Note:** As FDA currently does not have a published guidance on the validation of Alternate Microbiological Methods we followed the recommendations of the revised USP (b) (4) published in 2015, and (b) (4) published in 2013. Both of these documents consider the Method Suitability as independent of Method Validation.



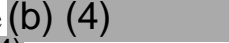
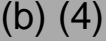
#### **Method Suitability:**

The method suitability studies were done using:

- (b) (4)

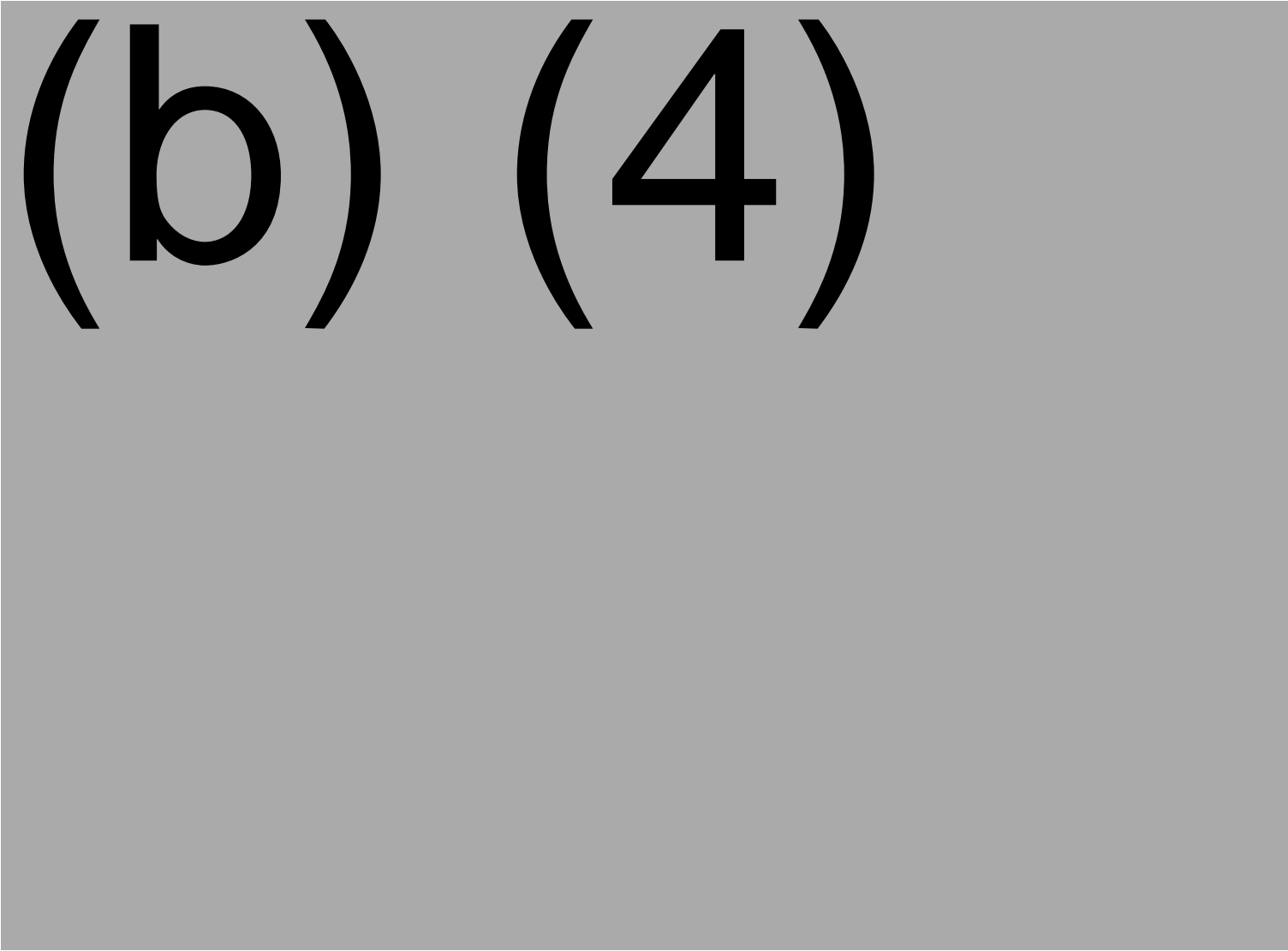
#### **Note:**

- a) (b) (4)

1. “All QC procedures for equipment and reagents used in this study are performed in accordance with approved written SOPs”
2. (b) (4)  

3. “In the event that criteria for valid tests as described by the manufacturer of the system are not met, any affected challenge sample will be (b) (4) 
4. “If none or only (b) (4) challenge sample is positive at (b) (4), the assay will be (b) (4) with new product test sample. The (b) (4) will be performed in (b) (4) 
5. “If none of the challenged product test samples are (b) (4) , the challenge will be (b) (4) with new product test sample and (b) (4) challenge organism concentration (b) (4) 

Data from the method suitability study are summarized in the table below.

(b) (4)



(b) (4)

*Reviewer Comments:*

- 1. The test microorganism panel used by the applicant includes a slow growing bacterium (b) (4), multiple facultative anaerobes, obligate anaerobe, yeast and mold – the used panel of microorganisms is broad and adequate.*
- 2. All inoculum levels were less than (b) (4) - the used inoculum level is same as used in the USP (b) (4) method and acceptable.*
- 3. For the ‘microorganisms only’ controls all microorganisms grew at their preferred growth condition. The obligate anaerobe, (b) (4) did not grow in the control aerobic media – this is acceptable.*
- 4. The obligate anaerobe (b) (4) took longer to grow in the presence of the by-product sample – this is not unexpected because the RBC of the by-product would introduce some oxygen in the media bottle and is not an issue for the actual sterility test as the detection time was less than (b) (4) in all cases.*
- 5. As all microorganisms (including the slow grower, (b) (4) grew in the presence of the test sample (b) (4) and within (b) (4) of inoculation (also, the two different media lots gave similar time of detection) we conclude that the proposed by-product test sample does not have a significant bacteriostatic/fungistatic effect on any of the microorganisms tested. Based on this data we also agree that the proposed (b) (4) incubation temperature (the applicant has updated their SOP-L0035 to reflect this incubation temperature – reference: STN 125594/0/4) and (b) (4) incubation period during the actual sterility test is appropriate.*

*Reviewer Comments on Other Issues:*

- 1. There is no possibility to repeat the sterility test as the proposed alternate sample is not stored.*
- 2. The applicant has confirmed that during the actual sterility test they will be using (b) (4) needles to inoculate both aerobic and anaerobic media (reference: STN 125594/0/4) – although this gauge size is not recommended (by (b) (4) for the inoculation of the anaerobic bottles it is acceptable in this case as the applicant was able to demonstrate the suitability of using (b) (4) needles for the inoculation of (b) (4) bottle (by successfully growing the obligate anaerobe, (b) (4) either alone or with the (b) (4) by-product).*

3. *The applicant has clarified (reference: STN 125594/0/4) that they will qualify all incoming lots of (b) (4) media by doing a (b) (4). The test bottles (and controls) will be inoculated with less than (b) (4) (microorganisms will be sourced from (b) (4)). Acceptance criteria are detection of (b) (4) (in (b) (4)) within (b) (4) of incubation (reference: STN 125594/0/4) – this is acceptable.*

#### **Sterility Testing Conclusion and Recommendations:**

1. *The proposed Sterility Test method and Release Specifications are acceptable.*
2. *As the applicant is not excluding Cord Blood units from antibiotic-treated donor mothers, we recommend that the HPC, Cord Blood label includes a warning regarding the potential of anaphylactic shock (for the sensitized recipients) from the residual antibiotics.*
3. *Due to*
  - *the inherent limitation of the sampling method used for the sterility test (especially under low bioburden conditions),*
  - *the fact that the processed HPC, Cord Blood final product is not suitable for terminal sterilization, and*
  - *the inability of the used media to neutralize residual antibiotics**we recommend that the Cleveland Cord HPC, Cord Blood not labeled as ‘sterile’ and the respective label include a warning regarding the potential to transmit infectious bacteria or fungi.*

#### **Identity Testing**

Identity testing includes ABO and Rh typing, and initial and confirmatory HLA typing.

#### **ABO Blood Group and Rh Typing**

##### **Description:**

A (b) (4) aliquot is used to perform the ABO Rh tube agglutination typing method. After (b) (4) the red blood cells with (b) (4) to remove any residual plasma and any other factors that may interfere with the antibody-antigen reaction, a (b) (4) red blood cell suspension is prepared. This provides the optimum antigen concentration for the tube agglutination method. Reagents containing Anti-A, Anti-B and Anti-D are added to the cell suspension to determine the different red cell antigens present. These sera will agglutinate cells with the corresponding antigens. No agglutination is a negative result and indicates the absence of the corresponding antigen.

A (b) (4) control is also tested simultaneously to check for instances when spontaneous agglutination, cold autoantibodies, or rouleaux, may interfere with testing and cause false-positive reactions. In the absence of agglutination with (b) (4) control, test results obtained with (b) (4) Blood grouping reagents may be considered valid. A positive reaction when red blood cells are tested with (b) (4) control indicates that positive reactions obtained with (b) (4) Grouping Reagents may be invalid. Further testing must be performed before a positive result can be interpreted.

The ABO/Rh Blood Group Typing reagents used by the applicant are FDA approved biologic products manufactured by (b) (4) .

The applicant takes part in American Proficiency Institutes (API) proficiency testing three times a year. Each proficiency challenge consists of five red blood samples sent to CCBC. These samples are tested for the A, B, and Rh antigens. Results are reported to API, and then a report card with the proficiency results are reported back to CCBC.

**Table 11: ABO/Rh Test results interpretation**

ABO/Rh GROUP	Cell Grouping			
	Anti-A	Anti-B	Anti-D	Gamma-clone Control
A+	Positive	Negative	Positive	Negative
B+	Negative	Positive	Positive	Negative
AB+	Positive	Positive	Positive	Negative
O+	Negative	Negative	Positive	Negative
A-	Positive	Negative	Negative	Negative
B-	Negative	Positive	Negative	Negative
AB-	Positive	Positive	Negative	Negative
O-	Negative	Negative	Negative	Negative

Technologist reproducibility is performed (b) (4) with all trained processing facility personnel as part of internal competency assessments (see details below)

#### **Technologist Competency assessment:**

For each processed cord blood unit, a set of maternal blood samples are sent to the (b) (4) for ABO/Rh typing results. Upon receipt of the ABO/Rh results from (b) (4) maternal samples are selected for testing in-house at CCBC. The in house ABO/Rh assay results are compared with the ABO/Rh from (b) (4). All processing facility technologists trained in ABO/Rh testing at CCBC are assessed on a (b) (4) basis to demonstrate competency.

(b) (4) test samples with known identity are received from the American Proficiency Institute. Three (b) (4) per year, on a rotating basis, one technologist is randomly selected to participate in the survey. The technologist performs the ABO/Rh testing on the (b) (4). The results are compared to data from other laboratories that participate in the survey and a report is generated by the American Proficiency Institute which assigns a grade.

#### **Reviewer's assessment:**

*The information provided in this section is sufficient.*

#### **HLA Typing (contract)**

##### **Description:**

For HLA typing an (b) (4) is inoculated with maternal, (b) (4) or frozen segment samples depending on the time of testing (initial or confirmatory). The (b) (4) is designed for



room temperature collection, shipment, archiving for future (b) (4)

#### **Initial HLA Testing:**

CCBC contracts with (b) (4)

#### **Confirmatory Testing (CT):**

When a confirmatory typing is requested, the HPC, Cord Blood is removed from the (b) (4)

The (b) (4) HLA laboratories are CLIA-certified and accredited by agencies such as ASHI, the (b) (4)

performs (b) (4)

Molecular results are entered electronically into the NMDP (b) (4) system by the contracted laboratory, (b) (4).

(b) (4) compares these results to the original HLA entered by the Cleveland Cord Blood Center. The CT results are reviewed by the Cord Blood Bank Director and compared to the original HLA results from (b) (4). Only HPC, Cord Blood that has its HLA identity confirmed by CT is made available for release to the transplant center. Any discrepancies are investigated by the (b) (4) department at (b) (4) and by the Quality Unit and Cord Blood Bank Director at CCBC.

#### **Reviewer comment:**

*The method description and validation are satisfactory because the testing labs are CLIA certified and ASHI accredited. CLIA regulations (42 CFR 493.1253) outline the requirements for establishment and verification of performance specifications, e.g. validation, for all tests used in CLIA certified testing labs. CCBC has provided the CLIA certifications and ASHI accreditation information for the contract laboratories.*

#### **Potency Testing**

Total Nucleated Cell count (TNC) is the primary potency test, but viable CD34<sup>+</sup> cell counts, TNC viability, and (b) (4) are also used as complementary tests for the evaluation of the quality and potency of a HPC, Cord Blood product.

## Total Nucleated Cell (TNC) Counts:

### Description:

The applicant performs total nucleated cell counts (WBC+NRBC) on the (b) (4) cell analyzer. This count is performed in (b) (4) to determine whether or not the total nucleated cell (TNC) number is high enough for processing. TNC number is calculated by adding the (b) (4). Products with TNC greater than (b) (4) are processed by (b) (4). After being processed, HPC, Cord Blood are (b) (4) and tested for total nucleated cell count (WBC+NRBC). At least (b) (4) TNC (absolute) at cryopreservation is required for clinical banking and licensed release.

### Equipment and materials:

Equipment: (b) (4)

Reagents: (b) (4) reagents are stored at room temperature. Once opened, the reagent expires after (b) (4).

(b) (4) hematology controls: Levels 1, 2 and 3, (b) (4), store upright at (b) (4). Once open, stable for (b) (4).

(b) (4) calibrator material: Provided by (b) (4) services.

### Equipment qualification:

- The (b) (4) cell analyzer is validated to read NRBC separate from WBC.
- The (b) (4) has preventative maintenance (PM) performed (b) (4).
- QC of (b) (4) background check will be within perimeter limits.
- (b) (4) low, normal and high controls are performed (b) (4)

Table 12: (b) (4) Manufacturer Stated Linearity

(b) (4)
---------

3 pages have been determined to be not releasable: (b)(4)

(b) (4)

***Reviewer Assessment:***

The (b) (4) is an FDA cleared device for complete blood count of peripheral blood samples. Although it's not cleared for counting cord blood samples specifically, the cell counts from the pre and post processing cord blood samples are within the range of the linearity of the device. Therefore, the reviewer determines that the above verification study is acceptable.

(b) (4)



This section reviews Volume 1-6 to assess Cleveland Cord Blood Center's product purity and potency flow cytometry assays. This includes:


- 1- Enumeration of CD34 Cells with (b) (4) and (b) (4) reagents using (b) (4) Protocol by (b) (4) (Volume 3, SOP L0010, pages 2-7)
- 2- Viability of TNC (Total Nucleated Cells).

This section also reviews the information submitted in response to telecom and email requests in STN 125594\0\3, STN125594\0\5 and STN125594\0\9.

**Lot Release Acceptance Criteria:**

- The minimum acceptable post-processing (b) (4) cell viability for an HPC, Cord Blood product is  $\geq 85\%$ .
- The minimum acceptable viable CD34<sup>+</sup> cell content of an HPC, Cord Blood product is  $\geq 1.25 \times 10^6$ .

(b) (4)



3 pages have been determined to be not releasable: (b)(4)

(b) (4)

*Reviewer's comment: Complete list of reagents and COAs was provided on the reviewers request in amendment STN 125594\0\3. COAs for (b) (4), CD34<sup>(b) (4)</sup> and (b) (4) were provided and reviewed.*

**Analytical Methods:**

(b) (4) is done according to SOP-L0010 A- (b) (4) CD34 (b) (4) and Analysis on (b) (4) (Original Submission-Volume 3, page 2).

**Instrument Setup:** (b) (4) instrument set up and QC is done according to the SOP-L0019. (b) (4) are included with each sample run to ensure application-specific setup, automated compensation, and (b) (4) quality control. (b) (4) levels of CD34 controls are tested (b) (4) when the flow cytometer is in use. Levy-Jennings graphs are



reviewed (b) (4) by the operating staff. Regular preventive maintenance is performed on the (b) (4) by the manufacturer's technical representative.

*Reviewer's comment: Levy Jennings plots (provided in response to (b) (4) were reviewed for (b) (4) and are acceptable.*

**Summary of the validation studies: (Volume 4, VAL-027, pages (1-16).**

**In this section we reviewed the data for accuracy, precision, linearity and range.**

**Accuracy:**

CD34: Test (b) (4) replicates using low CD34<sup>+</sup> cell controls (b) (4) and test (b) (4) replicates using high CD34<sup>+</sup> cell controls (b) (4) lots) from (b) (4).

**Precision:**

CD34<sup>+</sup> cell enumeration and viability: Test 3 cord blood samples low (b) (4) and determine CV, mean and standard deviation for viable CD34<sup>+</sup> cell enumeration.

(b) (4) viability: Test (b) (4) cord blood samples (b) (4) and determine CV, mean and standard deviation for TNC viability.

**Linearity and Range:**

CD34:

Study 1: Obtain Low and High controls for CD34<sup>+</sup> cell analysis of instrument range.

Run (b) (4) low and (b) (4) high controls on different days. Assess whether CD34 readouts are within expected control ranges. These controls are used for routine quality control of the (b) (4). Controls were tested on (b) (4) different days. All readouts were within expected low and high ranges. (Tables 1 and 2, attachment 1, VAL-0027-Volume 3).

Study 2: Use CD34<sup>+</sup> cells from high CD34 count (b) (4) CD34<sup>+</sup> cells/ $\mu$ L) from (b) (4) different post processed lots. Prepare (b) (4) and acquire in (b) (4) for CD34<sup>+</sup> cells count to establish limit of detection. This data is provided in STN 125594/0/9.

3 pages have been determined to be not releasable: (b)(4)

(b) (4)

#### Flow Cytometry Instrument Comparability Studies:

To assess correlation between CCBC (b) (4) cord blood samples were analyzed on (b) (4) instruments for CD34 and Lymphocytes. A linear regression statistical analysis was applied to the data to generate a correlation coefficient for each tested parameter. The (b) (4) met acceptance criteria by very strongly correlating with (b) (4) (correlation coefficient of (b) (4)). Expected correlation coefficient of (b) (4)

(b) (4)

*Reviewer's comment: There is only (b) (4) validated (b) (4) available at CCBC. However, there is (b) (4) flow cytometer at (b) (4) which is comparable to the CCBC but not validated. It was clarified with the applicant that*

HPC, Cord Blood tested at (b) (4), in the case of instrument malfunction at CCBC, will not be released under this BLA. These products will be released under IND(s).

### Proficiency Testing Programs:

CCBC participates in the proficiency programs from the College of American Pathologists (CAP) challenges. Tests performed on fresh cord blood samples, (b) (4). CCBC also participates in the (b) (4) fresh cord blood proficiency challenge, an (b) (4) mandated program in which one fresh cord blood sample is distributed (b) (4).

**Table 24: External proficiency testing at CCBC**

Method Proficiency Program	System Proficiency Program Design	Dates / Outcome Latest Test
Cell Counting, Viability, (Graded Results) College of American Pathologists (CAP)	(b) (4)	(b) (4) (b) (4) Acceptable
Cell Counting, Viability, (Educational Challenge) College of American Pathologists (CAP)	(b) (4)	(b) (4) (b) (4) Acceptable
Cell Counting, CD34 Analysis, (b) (4)	(b) (4)	(b) (4) Acceptable

These proficiency testing programs serve to confirm continued accuracy of the methods used by CCBC and competency of CCBC processing technologists performing the procedures.

*Reviewer's comment: Proficiency program is adequate at CCBC for CD34<sup>+</sup> cell enumeration, CD34<sup>+</sup> cell viability and TNC viability.*

### Operator Competency:

Technologist reproducibility is performed (b) (4) with all trained processing facility personnel as part of internal competency assessments. (b) (4) processed HPC, Cord Blood samples and (b) (4) quality control samples are randomly selected and gating strategies are applied by each staff member. All staff results are correlated and trended including average, standard deviation, and coefficient of variation. Additional training is provided if a technician falls outside the acceptable limits, and they are required to perform the assessment again. A CV of (b) (4) is expected among staff members. (STN125594/0/Vol.2 CMC\_31.4A page 80 of 102).

*Reviewers comment: (b) (4) competency assessments for technologists for gating strategy and data analysis with acceptable variability to be (b) (4) are adequate.*

**Overall Reviewer's Comments for Flow Cytometry:**

*The applicant has adequately validated the lab developed assays for CD34 cell enumeration and (b) (4) based CD34 and (b) (4) viability using flow cytometry. The testing personal is appropriately trained and laboratory has established external and internal proficiency testing for assay validation and operator variability. The SOPs for instrument validation, reagent qualification, and quality control of the assay are adequate to ensure the consistent performance of the flow cytometry assay as part of the manufacturing of HPC, Cord Blood product.*

## **RELEASE TO INVENTORY, SHIPPING, AND PREPARATION INSTRUCTIONS**

### **Release from quarantine to permanent storage**

Before release to searchable inventory, each HPC, Cord Blood is assessed via review and verification of acceptable outcomes for pregnancy and medical history, collection, handling and transportation. This review is performed by the Hospital Liaisons supervised by the CCBC Medical Director. Laboratory processing from receipt to cryopreservation and storage and the release testing is reviewed by the CCBC Director or designee. The CCBC Director reviews the batch records and the Quality Unit performs final review and confirms the final approval or rejection for release to inventory.



## **Registry listing:**

CCBC is a NMDP member for distribution of HPC, cord blood products. The entire inventory is listed with the NMDP Registry. Unlicensed units will be distributed under IND(s).

NMDP has developed the (b) (4) software system to simplify and standardize the HPC, Cord Blood registration and listing process. The (b) (4) system integrates data for all listed cord blood units into one comprehensive system covering data entry, confirmatory testing, searching, release, and adverse event tracking. It facilitates secure transmission of all data required for registration, including HLA tissue type information, infectious disease testing results, total volume, nucleated cell counts, CD34+ cell counts, collection date, unique NMDP identification number, and the medical history of the donor's mother and family.

After all required information has been entered, HPC, Cord Blood may be registered by selecting "Submit CBU for searching" at the bottom of the cord blood unit folder in the (b) (4) application. The Cord Blood Bank Director, or designee, different than the initial person who registered the HPC, Cord Blood unit, must first check all of the information entered into the (b) (4) application before making the HPC, Cord Blood unit available for search. The information will be checked for completeness, accuracy, and transcription errors. Once a final review of information has been completed, and has passed the quality check, the Cord Blood Bank Director, or designee, will change the HPC, Cord Blood status to "Available". The unit will now be available for search capabilities.

## **Cord blood Selection**

CCBC uses NMDP-assisted searching and selection procedures. As required, CCBC uses an (b) (4) contracted laboratory for confirmatory HLA typing to confirm and update the original typing.

Once a HPC, Cord Blood is identified for a potential transplant, the following three search stages will occur:

### **Confirmatory Typing (CT):**

Before it can be released for transplantation, the HLA typing of every HPC, Cord Blood unit must be confirmed by an independent testing laboratory. The requested unit for confirmatory typing is retrieved from the (b) (4) and an attached segment is removed for HLA typing and a separate segment is also removed for the (b) (4) and CD34<sup>+</sup> cell enumeration.

### **Cord Blood Unit requested to be Held (HE)**

A transplant center may request CCBC to hold a HPC, Cord Blood unit they have identified as a possible match for a patient. CCBC may hold that unit indefinitely, or until it is requested by another transplant center. Typically, a hold request occurs after the CT is completed and verified, but may occur prior to CT. CCBC will honor a hold request for (b) (4) days.

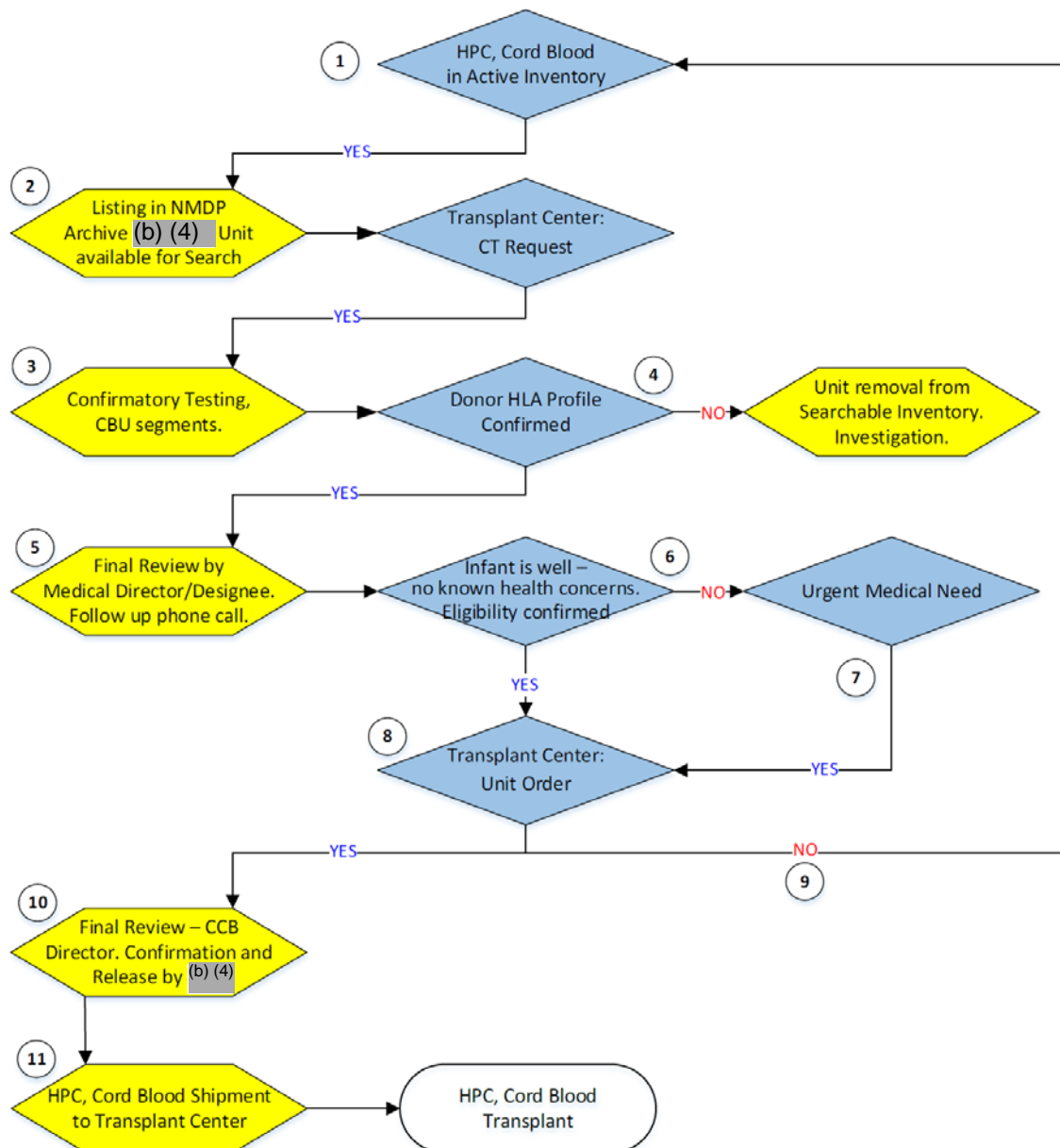
### **Cord Blood Unit requested for Order (OR)**

Once the confirmatory HLA typing for the HPC, Cord Blood and recipient are both completed and original results confirmed, the transplant center may order the HPC, Cord Blood for infusion. The transplant center completes a prescription for the HPC, Cord Blood and notifies the

Search Coordinator to activate the order in the (b) (4) system. The (b) (4) Search Coordinator then begins the process of requesting the proposed ship date, and target arrival date in advance of the planned infusion date established by the transplant center.

Prior to releasing the HPC, Cord Blood for transplant, the Medical Director and Cord Blood Bank Director must review the records, including the processing record, test results, donor medical history and screening records, and any donor follow-up information.

**Figure 10: Listing and Distribution for Transplant Flow Chart**





Note: Decision point #7 -The HPC, Cord Blood products that met all release criteria except donor eligibility requirements may be released under the “Urgent Medical Need” provision [21 CFR 1271.65(b)(1)(iii)] under IND(s).

*Reviewer’s Comment:*

*The selection procedure is acceptable.*

## **Shipping to Transplant Center:**

Procedures for unit shipment involve pre-cooling of the dry-shipper, preparation of the toe tag to be attached to the product, retrieval of the product from the (b) (4) and placement into the dry-shipper.

For the actual retrieval of the HPC, Cord Blood from the (b) (4), an empty Styrofoam sleeve is inserted into a red retrieval controlled rate freezer (CRF) device, which is then placed into one of two ports on the (b) (4) instrument containing the requested unit. The Retrieval Tab is selected on the computer that is connected to the (b) (4). After the unique product barcode has been entered or scanned in the unit ID area and "Enter" is pressed, the (b) (4) robot arm locates, and retrieves the selected product. HPC, Cord Blood inside the metal canister is removed from CRF device and placed inside a LN<sub>2</sub> vapor phase temperature monitored and maintained container.

The applicant charges and labels the validated dry shipper (b) (4) before the shipment. The temperature recording log is activated before the HPC, Cord Blood is placed to the shipper. Two staff members check the identifications and necessary documentations. The dry shipper is shipped to the transplant center by an approved logistic company with continuous tracking.

On arrival at the transplant center, the time, date and conditions of the shipper and HPC, Cord Blood are recorded. When the shipper is returned to CCBC, the temperature tracker data is downloaded and reviewed to verify that the temperature was maintained during shipping.

## **Shipping-dry shipper validation**

DMPQ reviewer Chad Burger reviewed and documented this validation. Please see his review for details.

## **Receipt and Storage Instructions:**

Detailed instructions for receipt and storage of HPC, Cord Blood are provided in the Prescribing Information that is distributed with the product.

## **Thawing and Emergency Recovery Instructions**

The applicant provides the detailed thawing and emergency recovery instructions with the package insert, which is shipped to the transplant center along with the HPC, Cord Blood. There are two thawing methods: Method one (Thaw and dilute) consists of two steps: 1) thawing; 2) reconstitution (dilution) with 145 mL of diluting solution. The recommended solution for product reconstitution/dilution is 5% human albumin and 10% Dextran 40 at (b) (4) ratio. The final

volume is 170 mL. Method two (Thaw, dilute and wash) includes washing and volume reduction by centrifugation for pediatric patients or adult patients who might be sensitive to fluid overload after the HPC, Cord Blood is thawed and diluted as described in method one.

### **Thawing and Cryoprotectant Removal Validation**

The applicant used [REDACTED] cryopreserved HPC, Cord Blood products for thawing [REDACTED]

The applicant also validated the thaw, dilute and wash procedure [REDACTED].

Acceptance criteria for both validation studies were established as follows:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



(b) (4)

***Reviewer's assessment:***

***The validation studies and data support the proposed post thaw shelf-life of four (4) hours at the temperature between 15 to 25°C.***

**RETENTION SAMPLES**

The applicant reserves multiple samples for future testing or for sample retention. However, HPC, Cord Blood (final product) samples are not retained when the banked product is distributed because limited quantity of cells are available in each HPC, Cord Blood lot, and typically the entire unit is administered to the patient.

**Maternal blood:**

1. [REDACTED]

**Cord Blood, (b) (4)**

[REDACTED]

**Cord blood, post-processing:**

1. (b) (4)
2. Final product - HPC, Cord Blood (after the addition of the cryoprotectant):
  - (1). (b) (4) for future testing.
  - (2) (b) (4) segments that are attached to the HPC, Cord Blood bag (these segments are no longer retention samples once the product is distributed because they are either used prior to the shipment of the HPC, Cord or still attached to the HPC, Cord Blood that is shipped to the transplant center).

***Reviewer's assessment:***

***The sample retention plan is acceptable.***

## PRODUCT STABILITY AND EXPIRATION DATING:

The applicant submitted available stability data using the HPC, Cord Blood that were banked from 2008 to 2012 (processed using the (b) (4) to establish the initial shelf-life of the product and the future stability testing plan to support the future extension of product shelf-life.

### 1. Stability data:

The applicant selected a total of (b) (4) HPC, Cord Blood banked from 2008 to 2012 to establish the initial expiration date.

(b) (4)

Frozen HPC, Cord Blood were thawed using a validated method (SOP L0053). TNC and CD34<sup>+</sup> cell viability was assessed by (b) (4), immediately after thaw. Table below shows the available preliminary post-thaw results for the (b) (4) samples.

(b) (4)

### *Reviewer's assessment:*

*The initial stability data is sufficient to support the proposed 5 years shelf-life of the CBUs manufactured by CCBC.*

### 2. Future stability testing plan:

For (b) (4), remaining units from the year that defined the initial expiry will be tested after a feasible and relevant period (e.g. 1 year before the initial expiration date expires).

**Parameters and acceptance criteria:**

Comparison of pre-freeze and post-thaw results for the following parameters and acceptable results are used to establish stability.



**Sample size and sampling strategy:**

For stability evaluation, three (3) HPC, Cord Blood will be randomly sampled from a designated pool of products that were manufactured using the same materials and processes as other HPC, Cord Blood units. CCBC is intent on using a strategy for selection of test samples representative of the composition of the entire bank, without need to sacrifice potentially highly valuable units for use in transplant (e.g. minority units). Consequently, for stability testing CCBC designates frozen products that have passed required lab specifications (i.e. units conforming with expected outcomes for all biological measures), but that cannot be released into inventory due to other issues that do not affect the physical and biological characteristics of the product (i.e. missing maternal history information).

***Reviewer's assessment:***

*The reviewer agrees with the sampling strategy and sample size proposed for (b) (4) of the HPC, Cord Blood post approval if supported by the study outcome.*

## **CONTROL OF ASEPTIC PROCESSING**

Please see CGMP review memo generated by the Division of Manufacture and Product Quality reviewer.

## **COMPUTER SYSTEMS AND VALIDATION**

Please see CGMP review memo generated by the Division of Manufacture and Product Quality reviewer.

## **LABELING AND TRACKING**

At the collection sites, the cord blood collection bag and the maternal specimens are labeled with an ISBT 128 Donation Identification Number (DIN) and hospital generated maternal

identification labels which include the birth mother's name, date of birth and medical record number. To maintain linkage between the cord blood unit and the birth mother, a hospital generated maternal label and a DIN label is placed on the maternal contact information page of CCBC UCB Collection and Maternal/Infant Data form (Form H0012a). To maintain confidentiality, the maternal contact information page is filed separately. Additionally, once the collected unit and the maternal specimens are received by the CCBC processing laboratory, the hospital generated maternal labels on the collection bag and the specimen tubes are removed after the identification information is reviewed and verified.

The sequenced ISBT 128 DIN barcode label sets are purchased from (b) (4). A DIN label is also placed on the consent form and all associated collection documents.

**Figure 11: Example of Collection Barcode Label Sets**



Each DIN set includes 20 DIN labels. The CCBC DIN consists of 13 characters, starting with a “w” followed by 12 digits. The first four digits (4215) is CCBC’s Facility Identifying Number (FIN). The next two digits represent the year of collection (e.g. 16 = 2016). The following two digits represent the specific collection site (20 for Piedmont, 21 for Emory, 38 for Hillcrest, and 39 for Fairview). The last 4 digits are numbered from 0001 through 9,999, enabling 9,999 unique product numbers per collection site per year. The flag code will be 01 by default for all cord blood units.

Example: W42151738123401= W4215 (CCBC FIN) + 17 (year 2017) + 38 (Hillcrest hospital) +1234 (serialized #) + 01 flag (single unit)

The cryopreserved HPC, Cord blood label include the product code S1393. Split units that are cryopreserved in 2 containers are identified with A0 and B0 after the product code. DIN labels with flag codes 41 through 45 are assigned to the maternal specimens.

**Reviewer comment:**

*In response to a filing letter request (letter dated 11/23/15, Amendment 3), the applicant explained that CCBC had implemented ISBT 128 labeling system from the beginning of the cord bank’s operation and they had chosen to assign a different Facility Identification Number (FIN) to each collection facility. The applicant was informed (email dated 12/22/2015) that a FIN assigned to the cord blood bank would be needed if they wished to use*

*the ISBT 128 identification and labeling system in lieu of an NDC. The ISBT 128 labeling information (with new FIN 4215) that is described above was submitted in Amendment 6 (CMC Section 31.4A, Rev. 2.0).*

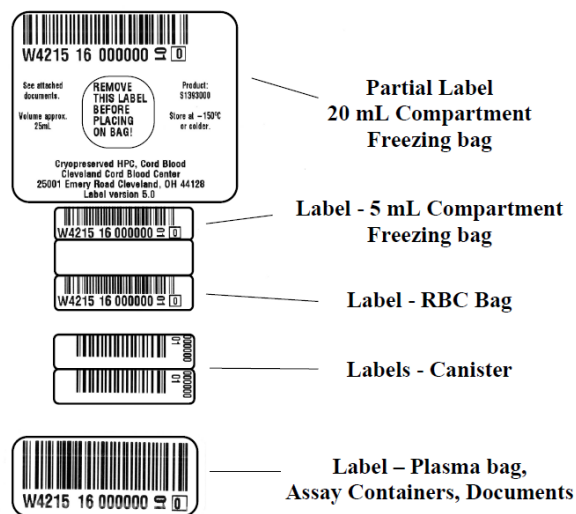
CCBC maintains accountability of the DIN labels used at the collection hospital on the Barcode Checklist Form. Unused DIN labels are affixed to the form which is maintained in the batch record (SOP-H0008 and form H0008a). For tracking purposes, the unit DIN is used on all containers, samples, forms and documents pertaining to collection, processing and distribution.

An NMDP identification number is also assigned to each unit and the maternal samples when the units are listed in the donor registry. The NMDP assigned numbers and the CCBC ISBT 128 numbers are documented on the HPC, Cord Blood Release to Inventory Form (WKS-L0028).

### Partial and Package Labels






The partial label is affixed to the cryopreserved HPC, Cord blood container, and at distribution, the full package label is attached to the canister with a tie-tag.

**Figure 12: Partial label affixed to the cryopreserved HPC, Cord Blood**



**Figure 13: Package label and attachment to the canister**



 W4215 16 000000 0		 6200	
Properly Identify Intended Recipient and Product		<div style="font-size: 2em; font-weight: bold; text-align: center;">A</div> <div style="text-align: center;">Rh POSITIVE</div>	
Collection Date/Time  01 Apr 2016 23:59 EDT (02 Apr 2016 03:59 UTC)		For Intravenous Administration See package insert for full prescribing information and instructions for preparation.	
Do Not Irradiate Do Not Use Leukoreduction Filter RX Only		 Expiration Date/Time 01 Apr 2016 23:59 EDT (02 Apr 2016 03:59 UTC)	
 51383000 HPC, CORD BLOOD Cryopreserved			
Approx 25 ml; < 5ml CPD 10% DMSO, 1% Dextran 40, 1% Hespan Store at -150 C or colder		Cleveland Cord Blood Center 25001 Emory Rd Cleveland OH License # 1234	

**Full  
Package  
Label**



*Reviewer comment:  
The above labels submitted in Amendment 6 are acceptable.*