MEMORANDUM

BLA 125407
CMC Review of Original Submission
HPC, Cord Blood

Duke University of School of Medicine, Carolina Cord Blood Bank

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

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PRODUCT SUMMARY

Proprietary Name: DUCORD

Proper/Non-proprietary Name: HPC, Cord Blood

Active Ingredient:	**UNII Code:**
CORD BLOOD HEMATOPOIETIC PROGENITOR CELLS	XU53VK93MC

Inactive Ingredients:	**UNII Code:**
DEXTRAN 40	K3R6ZDH4DU
DIMETHYL SULFOXIDE	YOW8V9698H
HESPAN	875Y4127EA
In Citrate Phosphate Dextrose:	
CITRIC ACID MONOHYDRATE	2968PHW8QP
PHOSPHORIC ACID	E4A8884NN
DEXTROSE	IY9XDZ35W2

Therapeutic or Pharmacologic Class: Allogeneic cord blood hematopoietic progenitor cell 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: W1582
The ISBT 128 product code: S1333

Intended Use:
Ducord is 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.

EXECUTIVE SUMMARY

Recommendation

We recommend approval of BLA 125407. The approval should be granted for Ducord lots manufactured after the approval date.

During our review of the sterility testing validation, we determined that the HPC, Cord Blood products originating from donors on intrapartum prophylaxis may contain residual antibiotics. Residual antibiotics may interfere with the sterility test, which could potentially increase the chances of transmitting bacterial and fungal infections. This concern is not particular to Ducord, since a significant number of cord blood donors are treated with intrapartum antibiotics. Thus, this issue must be solved for all HPC, Cord Blood products.

In support of our approval of Ducord, the safety data reviewed for this class of products (see FDA docket number 1997N-0497) has not indicated an increased incidence of microbial contamination with this class of products. However, we recommend that the label accurately reflect that while Ducord is tested for sterility, the test results may be indeterminate if the cord blood donor was treated with antibiotics. We also recommend that a warning should be put in the Ducord label regarding the potential of allergic reactions in antibiotic-sensitive Ducord recipients. The label was revised to include these concerns.

The applicant has requested that all HPC, Cord Blood units processed since 2001 be part of this biological license application (BLA). Based on the review of the application and inspection, the existing inventory does not meet license requirements because the applicant was not in compliance with CGMPs until the date of approval. The applicant submitted a major amendment during the review, extending the action date from July 9, 2012 to October 8, 2012. The major amendment contained important process and method validation information.

Product Overview

The product, Ducord consists of hematopoietic progenitor cells, cord blood (HPC, Cord Blood), which are minimally manipulated, unrelated placental/umbilical cord progenitor cells in cryoprotectant. Throughout this review the unprocessed cord blood will be referred to as cord blood or a cord blood unit (CBU) and processed (volume and RBC depleted) and/or cryopreserved cord blood products are referred to as HPC, Cord Blood or Ducord. The licensed product is referred to as Ducord. To conform to the Common Technical Document format the applicant has defined the cellular substance (3.2.S) as the HPC, Cord Blood up to the point when the unit is frozen, and the cellular product (3.2.P) as the HPC, Cord Blood after freezing.

This application describes the processes for donor screening, cord blood collection, processing, and release. Cord blood is processed using an ---(b)(4)--- method, which includes red blood cells and volume depletion. The ---(b)(4)--- process uses the ----------(b)(4)----------, which collects the hematopoietic stem cells, into an attached cryopreservation bag (cryobag). After processing, cryoprotectant (DMSO/Dextran 40) is infused into the cryobag, the bag is

overwrapped and cryopreserved in the Thermogenesis BioArchive® system. The product is stored at ≤-150°C in liquid nitrogen in a 2-compartment bag resulting in an 80/20 split, with three attached segments.

Ducord contains a minimum of 9 x 10^8 nucleated cells in a (b)(4) mL mixture of Citrate Phosphate Dextrose (CPD), 10% DMSO, 1% Dextran 40, and (b)(4) Hespan. CPD is ----------(b)(4)---------- and Hespan is added ----------(b)(4)----------; variable residual amounts of both are retained with the cells after processing. DMSO and Dextran 40 are added ----------(b)(4)----------. The cells have (b)(4) viability and a minimum of 1.25 x 10^6 viable CD34+ cells prior to cryopreservation (pre-cryopreservation). The nucleated cell count, ----------(b)(4)----------, and CD34+ cell count for each individual product is listed in the labeling information sent with each individual unit, for per kilogram dosing of Ducord.

Ducord products are uploaded to the National Marrow Donor Program (NMDP) registry, where inquiries are conducted through the NMDP program database, CordLink. Upon request, Ducord HLA type is confirmed and Ducord is released for shipment to the transplant center. Ducord is shipped to transplant centers in "Dry Shippers that maintain temperature at ≤-150°C. All post-transplant follow-up, including adverse events (AEs), is obtained by the applicant through the CIBMTR (Center for International Blood and Marrow Transplant Research). Details regarding each of these steps in the process were provided in the original BLA submission or subsequent amendments and are reviewed in relevant sections below.

Expiration date
The stability data analysis provided in Amendment 013 (August 10, 2012) supports a seven (7) year expiry date. In addition, the applicant has a stability protocol in place for determining if the expiration date can be extended on a (b)(4) basis (see stability section of this review for details). The final version of the Quality System approved stability protocol was submitted in amendment 021 on October 2, 2012.

Review Findings
During the review process deficiencies were identified and communicated to the applicant. Major deficiencies included insufficient process and method validation plans and data, incomplete donor eligibility screening, and an inadequate stability program to establish and extend the expiration date. These deficiencies were also cited on the 483 observation report that resulted from the February 2012 pre-approval inspection. These deficiencies have been corrected as outlined in various sections of this review. During our review of the sterility testing validation, we also determined that the HPC, Cord Blood products originating from donors on intrapartum prophylaxis may contain residual antibiotics, which may interfere with the sterility test. This concern is not particular to Ducord, since a significant number of cord blood donors are treated with intrapartum antibiotics. Thus, this issue must be solved for all HPC, Cord Blood products.

GENERAL INFORMATION

The Duke University School of Medicine (Duke) has applied for a biological license to distribute Ducord. Ducord is manufactured by the Carolina Cord Blood Bank (CCBB) processing

laboratory, which is a functional part of Duke. CCBB and Duke are used interchangeably throughout this review.

Processing facility: All Ducord products are processed and stored at the Carolinas Cord Blood Bank Processing Laboratory (CCBB), North Pavilion Building, 2400 Pratt Street, Durham, NC 27705.

Cord Blood Collection sites: Cord blood units (CBU) are collected from the 8 fixed collection sites listed below. All sites are located in North Carolina except one located in the Boston area. Local sites are located within 50 miles of CCBB. The Applicant is also planning to license qualified HPC, Cord Blood obtained from non-fixed sites (throughout USA). Cord blood is obtained from non-fixed sites using the cord blood collection "Kit Program," which is described in detail in the collection section of this review.

TABLE 1: CCBB FIXED CORD BLOOD COLLECTION SITES

Site Code	Site	Address/Phone	Local/remote
DU	Duke University Hospital (site #21)	2100 Erwin Road, Durham, NC 27705 Phone: 919.681.037	Local
DRH	Durham Regional Hospital (#22)	3643 N. Roxboro Road , Durham, NC 27704 Phone: 919.470.829	Local
UNC	Memorial Hospital at the University of North Carolina- (#23)	10 1 Manning Drive, Chapel Hill, NC 27599 Phone: 919.843.0918	Local
REX	Rex Hospital (#49)	4420 Lake Boone Trail, Raleigh, NC 27607 Phone: 919.784.2276	Local
WHG	Women's Hospital of Greensboro (site #70)	801 Green Valley Road, Greensboro, NC 27408 Phone: 336.832.4836	Local
WAMC	Womack Army Medical Center (s #90)	2817 Reilly Road, Ft. Bragg, NC 28310 Phone: 910.643.2517	Remote
BWH	Brigham and Women's Hospital (#30)	75 Francis Street, Boston, MA 02115 Phone: 617.632.2434	Remote
CMC	Carolinas Medical Center (#61)	920 Church St. North, Concord, NC 28025 Phone: 704.403.6687	Remote

Testing Laboratories: CCBB uses a number of contract laboratories (see Table 2) to perform safety and characterization testing on Ducord and related materials. Some of these labs are registered with the FDA and all are CLIA certified.

TABLE 2: DUCORD TESTING LABORATORIES

Test	Contract Testing Organization	Certification(s)
Infectious Disease Testing	----------(b)(4)----------	----------(b)(4)----------
Sterility Testing	CCBB Processing Laboratory North Pavilion Building Suite 1400 2400 Pratt Street Durham, NC 27705 Phone: 919.668.2066	CLIA# 34D1005310 FEI# 3002663011
Human Leukocyte Antigen Typing Initial	(b)(4)----------	---------(b)(4)---------
Confirmatory HLA	----------(b)(4)----------	---------(b)(4)---------
---(b)(4)--- and CD34+ Assays	Duke Stem Cell Laboratory (SCL) North Pavilion Building, Suite 1300 2400 Pratt Street Durham, NC 27705 Phone: 919.668.1170	CLIA# 34D1005310 FEI# 3002663011
Hemoglobinopathy Assays	(b)(4)---------- ---------- -(b)(4)----------	---------(b)(4)--------- ---------(b)(4)---------

BACKGROUND/HISTORY

CCBB was established in 1997, and at the time of the BLA submission had issued over (b)(4) barcodes for cord blood units (CBU) collected, (b)(4) CBU met initial volume, 50% of those failed Total Nucleated Cell Count (TNCC) or volume ((b)(4)). Of the (b)(4) units processed, (b)(4) met release specifications; and of these, 4500 were disposed of following additional tests

(e.g., donor safety, CD34+ counts, sterility, etc). About 1500 HPC, Cord Blood units have been transplanted, leaving about (b)(4) in storage at CCBB at the time of BLA submission.

CCBB had a Pre-BLA meeting with the agency in October of 2010 as well as additional communications related to validation of sterility testing by the --(b)(4)-- method. The BLA was submitted on September 9, 2011. Several amendments have been submitted following discussions with the review team. The Applicant submitted a major amendment (125407-008) on June 1, 2012, extending the review clock for 90 days to October 8, 2012. Amendments 010 (June 27, 2012) and 012 (July 30, 2012) included responses to additional information requests. Amendment 013, received on August 10, 2012 contained the stability protocol and revised summary of stability data as well as SOPs and text revisions. Amendment 014 received on August 15, 2012 and Amendment 015 received on August 16, 2012 contained additional responses to information requests. Amendment 016 was received August 17, 2012 and contained labeling and prescribing insert clarifications and revised SOPs for product distribution. Amendment 017, received August 31, 2012, contained additional labeling information and a request for exemption under 21 CFR 201.25(d)(ii) from the NDC barcode label requirements, and additional information for the stability protocol. Amendment 018, received September 21, 2012, contained revised labeling information, and a commitment for adverse event reporting. Amendment 019 submitted in September 24, 2012, included revised stability protocol acceptance criteria and validation of the ---(b)(4)--- thawing procedure to be used in the stability protocol to extend expiry date. Amendment 020 received September 25, 2012 contained the final version of the Prescribing Insert label, container labels and response to 483 observations. Amendment 021 submitted October 2, 2012 contained the Prescribing Insert label with Instructions for Preparation for Infusion, final versions of the package labels and a revised stability protocol (applicant also submitted this information by email).

FACILITY DESCRIPTION AND FLOOR DIAGRAMS

Carolinas Cord Blood Bank (CCBB) Processing Laboratory:

The CCBB Processing Laboratory was commissioned in September 2008. The area used for processing was described in detail and floor diagrams of the general layout of the facility were submitted. Material, product and personnel flow directions were sufficiently detailed to determine that the space was adequate for intended manufacturing operations (see DMPQ review for detailed analysis of facility and equipment qualification). Briefly, all Ducord processing occurs in the CCBB Processing Laboratory, which occupies approximately (b)(4) square feet of dedicated cell processing laboratory space on the plaza level of the North Pavilion Building, Suite (b)(4) at 2400 Pratt Street Durham, NC 27705. In addition, the CCBB has approximately (b)(4) square feet of freezer space located on the -(b)(4)- floor, Room (b)(4) and Room (b)(4) of the North Pavilion Building. A supply room is also located on the ground floor. CCBB has dedicated laboratory space that is divided into 6 main manufacturing areas: receiving, prequalification, processing, post-processing counts and sample preparation, cryopreservation, long-term storage, and shipping preparation. There is also an area for storage of supplies that have been release from quarantine. The Duke Hospital Stem Cell Laboratory (SCL), the site of some in process testing (e.g. flow cytometry, hematopoietic progenitor cell (b)(4) assays, stability testing) is located across the hall from the CCBB processing laboratory. Additional

administrative, filing, and scanning space is located on the (b)(4) floor of the North Pavilion Building and at an administrative building ----------(b)(4)----------.

Collection facilities: The CCBB has fixed collection areas in the specified collection locations (Table 1), and personnel are trained by CCBB for aseptic cord blood collection *in utero* and *ex utero*. Collection space includes a scale, stand, cleaning and collection materials, as well as temperature controlled storage (see review of collection for details). Duke also accepts CBUs from non-fixed sites using a pre-packaged kit (Kit Program) and medical personnel trained in cord blood collection via an online course. Please see review of collection procedures for additional details.

CCBB processing capacity summary: ----------

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

----------.

Findings at inspection: The Pre-Market Inspection was held Feb 27-March 2, 2012. See PMI/EIR report by DMPQ for details. Briefly, relevant CMC 483 observations included: validation of manufacturing process and QC methods were not complete and there was no Quality Unit approved stability protocol in place. These items have been addressed and are discussed in relevant sections of this review.

CONTROL OF ASEPTIC PROCESSING

Duke has several procedures in place to prevent contamination and cross-contamination during collection, processing and testing, which were detailed in Appendix A (see DMPQ review of aseptic process validation/media fill). Briefly, each donor is screened for eligibility based on medical history and risk of infectious disease before any cord blood is collected (see Collection Process description and DE sections); maternal samples are tested for infectious diseases; and each donor's records are reviewed for donor eligibility prior to banking. All staff involved in collection and processing of cord blood are trained in aseptic technique. Staff training also includes chain of control procedures and labeling requirements, which are in place to reduce the risk of contamination. CBUs are also segregated during collection and processing, such that only one CBU is handled at a time by trained personnel. As an added control measure, labels are checked prior to and following each step in the manufacturing process.

Collection sites and the CCBB Processing Laboratory are disinfected regularly (cleaning validation process reviewed by DMPQ) and the facilities and associated equipment are cleaned between samples. Each CBU is tested for sterility. A negative sterility test result is required for Ducord release (see Sterility Testing section). Any CBU that tests positive is immediately removed from storage and discarded. Any CBU that yields a positive result for growth is tested

in the Duke Hospital Clinical Microbiology Laboratory for further identification and sensitivities. The CCBB Quality Unit reviews manufacturing records for sterility failures to determine potential trends related to sterility issues during the manufacturing process.

DUCORD DESCRIPTION AND CHARACTERIZATION

Duke has cited the clinical efficacy data from the FDA docket number 1997N-0497, and has set Ducord product release specifications that meet or exceed the safety, purity and potency for HPC, Cord Blood products as outlined in the FDA Guidance for industry: Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications (October 2009). Ducord contains a minimum of 9 x 10^8 nucleated cells in a (b)(4) mL mixture of Citrate Phosphate Dextrose (CPD), 10% DMSO, 1% Dextran 40, and (b)(4) Hespan. CPD is --------(b)(4)---------- and Hespan is added ----------(b)(4)----------; variable residual amounts of both are retained with the cells after processing. DMSO and Dextran 40 are added ----------(b)(4)----------. The cells have ---(b)(4)- viability pre-cryopreservation and a minimum of 1.25 x 10^6 viable CD34+ cells. The nucleated cell count, ----------(b)(4)----------, and CD34+ cell count for each Ducord product are listed in the labeling information sent with each product so that per kilogram dosing of Ducord can be calculated. Ducord is frozen and stored at ≤-150 ºC in a 2-compartment bag resulting in an 80/20 split. The compartments can be accessed separately, if needed. Once thawed, Ducord is liquid with a pink to red color. Ducord is shipped in a Dry Shipper that has been validated to maintain proper storage temperature of ≤ -150 ºC for up to 48 hrs past delivery date (or for a maximum of 8 days). See Shipping summary below and DMPQ review. Ducord release specifications and acceptance criteria are outlined in Table 3 below.

TABLE 3. RELEASE SPECIFICATIONS FOR DUCORD

Product Characteristics	Testing	Sample (Type and Timing)	Specifications from 2009 FDA Guidance	Ducord Acceptance Criteria
Safety	Infectious diseases – Testing Required. (21 CFR 1271.45 through 1271.90)	Maternal peripheral blood obtained within 7 days of cord blood collection – Type and Timing Required. (21 CFR 1271.80(a) and (b))	All tests negative except non-treponemal test for syphilis when confirmatory test is negative.	All tests negative, except for anti-CMV
			CMV - Report	If CMV antibody positive, unit must be negative by validated (b)(4) assay (----------(b)(4)----)
	Sterility - Bacterial and fungal cultures – Testing Required.	HPC, Cord Blood (pre-cryopreservation) *	No growth (21 CFR 211.165(b), and 21 CFR 610.12)	No Growth by validated sterility assay (---(b)(4)---)

Product Characteristics	Testing	Sample (Type and Timing)	Specifications from 2009 FDA Guidance	Ducord Acceptance Criteria
	Hemoglobin	Cord blood** or appropriate donor sample obtained at time of cord blood recovery	No homozygous hemoglobinopathy	No disqualifying abnormal homozygous hemoglobin or disqualifying double heterozygous hemoglobins
Purity and Potency[1]	Total nucleated cells (TNC)	HPC, Cord Blood (pre-cryopreservation)	≥ 5.0 x 10^8 TNC ***/ unit HPC, Cord Blood	--------(b)(4)-------- --------(b)(4)--------
	Viable nucleated cells	HPC, Cord Blood (pre-cryopreservation)	≥ 85% viable nucleated cells	(b)(4) viable nucleated cells ------(b)(4)--------
	Viable CD34+ cells (flow cytometry)	HPC, Cord Blood (pre-cryopreservation)	≥ 1.25 x 10^6 viable CD34+ cells ****/ unit HPC, Cord Blood	CD34+: ≥ 1.25 x 10^6
Potency	--------(b)(4)-------	----------(b)(4)----------	--(b)(4)--	-----(b)(4)-------
Potency	----------(b)(4)----------	----------(b)(4)----------	--(b)(4)--	--(b)(4)--
Purity	--------(b)(4)-------	----------(b)(4)----------	--(b)(4)--	---------- ----------(b)(4)---------- ---------- ----------
Identity	Initial Human leukocyte antigen (HLA) Typing	Cord blood	Report	Report
	Confirmatory HLA	Attached segment of HPC,cord blood	Confirms initial typing	Confirm
	Blood Group/Rh Type	Cord blood	Report	Report
Identity	Gender	Cord Blood	Report	Report
Volume	Cord blood volume at collection	Cord blood	Not listed	-(b)(4)- for minority donor or -(b)(4)- for Caucasian donor

Ducord acceptance criteria listed in blue text are more rigorous than the specification required by the 2009 FDA Guidance.

[1]Other purity and potency assays may be considered under the BLA

* Sample may be obtained before or after addition of the cryoprotectant.

** Cord blood = a sample of unmanipulated cord blood. A red cell sample or other cord blood aliquot obtained after volume reduction may be used for testing with appropriately validated reagents or test systems.

*** Based on 20 kg recipient, a target dose of ≥ 2.5 x 10^7 nucleated cells/kg and ≥ 70% post-thaw recovery = 1.7 x 10^7 nucleated cells/kg.

****Based on CD34+ cells ≥ 0.25% of TNC prior to freezing.

DONOR ELIGIBILITY

CCBB's donor eligibility procedures include screening and testing of the cord blood donors for risks of relevant communicable diseases or disease agents (RCDAD). For the initial pre-screening prior to the collection of collect blood, birth mothers are assessed for the risk factors outlined on CCBB-COL-002 FRM 1, including:

- Prior positive results for HIV, Hepatitis B & C, Tuberculosis (positive skin test for TB without having received BCG vaccine)
- Active sexually transmitted disease
- Known risk behaviors (tattoo or body piercing in the past 12 months with shared or non-sterile instruments, used needle to take drug not prescribed by physician in the past 12 months)
- --(b)(4)-- in the past 12 months
- Vaccination or shots in the past 12 months (HBIG, smallpox, oral polio, yellow fever, chicken pox, MMR or nasal flu vaccine, unlicensed vaccine, rabies vaccine following a bite by a rabid animal or one suspected to be rabid)
- Deferred as a blood donor due to a history of risk behavior for transfusion-transmittable disease
- Mother used an egg and/or sperm donor and medical history of the donor is not available or unable to verify that the egg/sperm was obtained from an AATB accredited bank.

The process for the initial qualification and screening of the birth mother at the fixed and non-fixed collection sites (referred to as Kit Program) are summarized in the Donor Screening section below.

Donor Screening

The donor screening process includes the review of the birth mother's and the infant donor's relevant medical and physical examination records, and the maternal medical and family medical history questionnaires to identify RCDAD risks factors. If the maternal medical and family history questionnaires (SOP CCBB-COL-005, ver. 6, CCBB-COL-005 FRM 2 and CCBB-COL-005) are completed more than 14 days prior to the cord blood collection, the responses are reaffirmed during the follow-up review. Risk factors identified during the review of the donor questionnaires may result in the donor being deferred or determined to be ineligible.

A. Birth mother pre-qualification and screening at fixed collection sites

Trained CCBB collection staff or trained hospital staff is responsible for obtaining consent from the birth mother and performing the initial donor qualification. Birth mothers who have passed the initial qualification are interviewed by the trained staff for completing the medical risk and family history questionnaires. In certain cases, the questionnaires may be self-administered but staff conducts a follow-up review to verify the answers. The information regarding RCDAD risk factors identified during the review of clinical and physical examination records are documented at the time of delivery (SOP CCBB-COL-002, CCBB-COL-08 FRM 1, and CCBB-COL-07 FRM 2). The donor

consent, completed questionnaires, and the completed delivery forms are sent to the CCBB with the collected units.

B. Birth mother pre-qualification and screening at non-fixed collection sites (Kit program)

Potential donors are pre-qualified over the phone. If the birth mother meets the initial acceptability criteria, the collection kit which contains the donor consent and questionnaires are sent to the mother around the 34-36th week of pregnancy. The completed forms are shipped to CCBB with the collected cord blood unit (SOP CCBB-COL-013). Within 60 days of receipt of the collected unit, CCBB staff contacts the birth mother to conduct a verbal review and confirmation of the consent and the maternal risk and family history questionnaires. The follow-up interview includes verification of the information regarding identification of risk factors for sepsis in the infant 24 hours after birth (SOP CCBB-COL-018 and CCBB-COL-018 FRM1).

Donors are screened for the following risk factors: HIV 1/2, HTLV I/II, HBV, HCV, Syphilis, WNV, Sepsis, Vaccinia, TSE (CJD/vCJD), Xenotransplantation. Additionally, donors are screened for ---(b)(4)--- Chagas ---------(b)(4)---------- which are not currently required by the FDA.

Reviewer Comment: *The documents in the original submission did not include clear instructions for the review and documentation of the clinical and physical evidence for RCDADs. The instructions for the review of the relevant medical and physical examination records was added to the revised documents (CCBB-COL-07 FRM 2 and CCBB-COL-016 FRM2) that were submitted in amendment 013 on 8/10/12.*

Additionally CCBB has established a "Look Forward" program to follow-up with birth mothers to clarify information and to determine subsequent diseases in the mother or infant which could adversely affect a cord blood recipient (SOP CCBB-COL-028 and CCBB-COL-028 FRM1). The information obtained through the follow-up may result in discard of the unit.

Donor testing

Infectious disease tests (see Table 4) are performed at ----------(b)(4)----------. The contract testing laboratory (See Table 2) is registered with the FDA (-------(b)(4)--------) and CLIA certified (------(b)(4)------). The Applicant has submitted the testing laboratory's staff training and competency assessment procedure. The testing laboratory participates in proficiency testing program and test samples are rotated among the laboratory testing staff. The results of the proficiency tests are reviewed by quality control reviewer and manager. The QA team at CCBB conducts periodic audits of the --(b)(4)-- to ensure compliance with the requirements.

Maternal blood specimens for donor testing are obtained on the day of or within 7 days of the infant's birth (SOP CCBB-COL-025). For collections at fixed collection sites, specimens are packed on ice in a shipping container and sent from the collection hospitals to CCBB. For collections at non-fixed sites (kit program), the maternal blood specimens are placed with the

collected cord blood unit in the collection kit container which is shipped from the collection facility to CCBB. The blood collection tubes are labeled with a unique identification number (ISBT barcode label- refer to the Cord Blood Donor Tracking for additional information). CCBB sends the maternal blood specimens to ---(b)(4)--- following the testing laboratory's shipping procedure and tracks the receipt and shipment of all specimens. A second set of maternal blood samples remains in the CCBB and are processed and stored according to SOP CCBB-LAB-021. Samples from non-fixed sites must accompany the CBU or the unit is discarded.

Reviewer comments: *The original SOP CCBB-COL-025 and shipping forms referred to "----(b)(4)---- collection sites" and shipment of ---(b)(4)---. At the request of the reviewers, all references to the shipment of ---(b)(4)-- were removed from applicable SOPs and forms. Revised documents were submitted on 6/1/12 in amendment 008.In the SOPs submitted in the original application, there was no information regarding the assessment of birth mothers for the possibility of plasma dilution prior to obtaining the maternal blood specimens. The revised SOP CCBB-COL-025 submitted on 6/1/12 states that maternal specimens will not be collected from birth mothers that have received >2000ml intravenous fluid within 1 hour or blood transfusion with 48 hours of specimen collections. The revised SOPs and forms are acceptable.*

The following are the current tests performed using FDA-licensed, approved or cleared test kits, in accordance to the manufacturer's instructions.

TABLE 4: DONOR INFECTIOUS DISEASE TESTS

Test	Test kit Manufacturer	Test Method Description	Approval #
Anti-HBc	-------(b)(4)---- ----------	---------- ----------(b)(4)---------- ---------- ----------	----(b)(4)----
HBsAg	----(b)(4)----	---------- ----------(b)(4)---------- ---------- ----------	----(b)(4)----
Anti-HCV	----(b)(4)----	---------- ---------- ----------(b)(4)---------- ---------- ----------	----(b)(4)----
Anti- HIV 1 & 2	-------(b)(4)---- ----------	---------- ---------- ----------(b)(4)---------- ---------- ----------	----(b)(4)----
Anti- HTLV I & II	----(b)(4)----	---------- ---------- ----------(b)(4)---------- ---------- ---------- ----------	----(b)(4)----
Anti-*T. cruzi* Assay (Chagas' Disease)	----(b)(4)----	---------- ---------- ----------(b)(4)----------	----(b)(4)----

Test	Test kit Manufacturer	Test Method Description	Approval #
		---------- ----------	
NAT HIV/HCV/HBV	----(b)(4)----	---------- ---------- ----------(b)(4)---------- ---------- ---------- ----------	----(b)(4)----
NAT WNV	----(b)(4)----	---------- ---------- ----------(b)(4)---------- ---------- ----------	----(b)(4)----
Treponema pallidum (Syphilis)	----(b)(4)----	---------- ---------- ---------(b)(4)---------- ----------	---------- --(b)(4)------ -----
Anti-CMV	----(b)(4)----	---------- ---------- ----------(b)(4)---------- ---------- ----------	---------- --(b)(4)------ -----

Reviewer's comments: *The above infectious disease tests are performed using FDA-licensed, approved or cleared donor screening tests in accordance with the manufacturer's instructions in a CLIA certified testing laboratory. Several SOPs in the original submission referred to (b)(4) for syphilis testing. In the response letter submitted on 2/21/12 (amendment 5), the Applicant clarified that (b)(4) testing was performed in the past but the -------(b)(4)------ donor screening test (----------(b)(4)----------) is the current test. Revised SOPs CCBB-COL-002 and CCBB-COL-025 were submitted on 6/1/12 and CCBB-LAB-018 on 8/10/12.*

In addition to the above tests, Applicant performs CMV -(b)(4)- for donors that test positive for CMV antibody.

Note: *The CMV (b)(4) assay is performed by the cell processing laboratory. Refer to the Lot Release section for the method description and validation.*

CCBB does not release HPC, Cord Blood units into the search inventory from birth mothers who are positive for any of the above tests except for CMV. CMV results are reported to the transplant center but the results are not factored into the donor eligibility determination. Also HPC, Cord Blood from donors with positive CMV total antibody and positive or intermediate CMV (b)(4) results are not released for clinical use.

Reviewer comment: *Several SOPs in the original submission referred to confirmatory testing for donors who test positive for anti-HBc and HTLV I/II and syphilis. In the response letters submitted on 2/21/12 and 6/1/12, the Applicant stated that the confirmatory tests are performed by the testing laboratory following their established SOPs for donor notification purposes. However, CCBB does not factor in the results of the confirmatory tests into the DE*

determination. Donors with initial positive screening test results are designated as "Hold for Further Testing" in the --(b)(4)--- system and are not released in to the search inventory but may be retained for research use. The issue was addressed in SOPs CCBB-COL-002 and CCBB-COL-020, submitted on 6/1/12 (amendment 008) and SOP CCBB-COL-018 submitted on 8/10/12 (amendment 013).

Final donor eligibility determination

HPC, Cord Blood is maintained in quarantine until all the donor screening and testing results are reviewed and the donor eligibility has been determined (SOP CCBB-QA-045). CCBB 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). Only HPC,Cord Blood from eligible donors are accepted for licensure.

Reviewer comment: *Donors with certain risk factors identified during the donor screening are deemed ineligible and will not be included in the licensed inventory. However, these units may be released for clinical use under IND, if there is a documented urgent medical need.*

The final donor eligibility determination is performed by the Medical Director and documented on the Exclusion and Quarantine Release Form (CCBB-QA-045 FRM1) prior to the release of HPC, Cord Blood into the search inventory. The Medical Director documents whether the unit is acceptable for licensure or for release under IND. The final approval for release of a unit into the search inventory is performed by the Quality System Unit.

When a Ducord unit is distributed to the transplant center, the summary of records including the list of infectious disease test results and the final donor eligibility determination accompanies the product.

Reviewer comment: *The SOPs submitted in the original application did not clearly define the process for the final donor eligibility determination. The Applicant addressed the issue in SOP CCBB-QA-045 that was submitted on 6/1/12 and the revised form (CCBB-QA-045 FRM1) received on 8/10/12. The donor eligibility determination is performed in accordance with the regulatory requirements.*

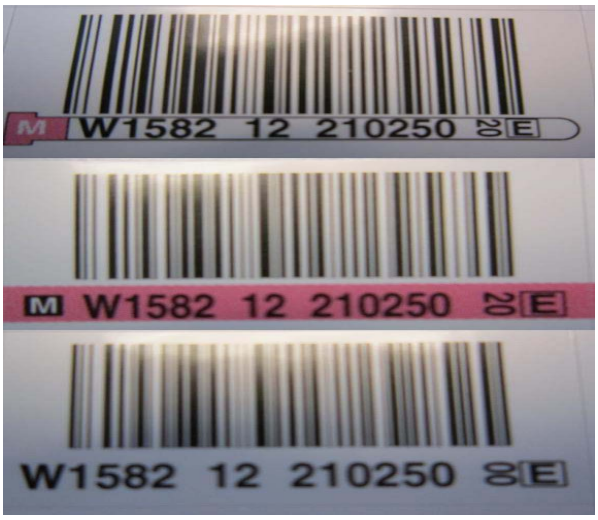
Cord Blood Donor Tracking

The birth mother's identity (name, date of birth and hospital number) is documented on the Volunteer Blood Donor Identification forms (Fixed sites: CCBB-COL-007-001 FRM 1 and FRM 3, Kit program: CCBB-COL-007 FRM 2). A donor identification number assigned to each collected unit and the maternal specimens is placed on each form to maintain linkage between the birth mother and the donor.

CCBB uses the ISBT 128 data structure for the donor identification number that is included on the cord blood collection bag and the final cryopreserved HPC, Cord Blood container labels. The ISBT 128 number includes the facility ID number, year and 6-digit serialized unique identifier. The same number with prefix "M" is assigned to the birth mother (maternal

specimens). To further distinguish the maternal identification number, the maternal ISBT barcode labels have a pink strip or a pink M (as outlined in response letter dated 5/31/2012 (amendment 008).

Figure 1: Sample ISBT ID label



Facility ID# (W1582) + Year (12) + serialized ID# (210250)

The unit ID# is also included on all the processing records, associated retained samples, product container labels, test result reports, registry database and all the unit reports provided to the transplant centers. The donor identification number allows tracking from the donor to the recipient and vice versa.

***Reviewer comment**: The described unique donor identification and tracking method is acceptable.*

***Additional reviewer notes:** In amendment 6, the Applicant requested licensure of units collected from September 29, 2008. Licensure of units banked prior to the approval date is not recommended. The following are the reviewer's assessment regarding the status of units in the existing inventory based on the collection and donor eligibility procedures:*

- *Adequate procedures for assessments of the birth mother for the possibility of plasma dilution were not implemented until May 23, 2012 (CCBB-COL-025).*
- *Adequate procedures for review of the donor medical and physical examination records were not implemented until 8/20/12 for the collections at fixed sites (CCBB-COL-007 FRM2).*
- *Adequate procedures for documentation of the final donor eligibility before the release of units into the search inventory were not implemented until May 24, 2012 (CCBB-COL-025).*
- *The Applicant did not reject units based on out of range transportation temperature or time until 8/12/2012 when the revised SOP CCBB-LAB-017 was implemented.*

CORD BLOOD COLLECTION

Carolina Cord Blood Bank (CCBB) performs cord blood collections either at designated hospitals (fixed sites), or at collection sites without a pre-existing agreement with CCBB. These sites are referred to as the "Kit Program" (non-fixed sites). Cord blood collections may be performed in *ex-utero* or *in-utero* during vaginal or c-section deliveries.

Collections at Fixed Sites

CCBB has established contracts with 5 designated local hospitals in NC (2 in Durham, 1 in Chapel Hill, 1 in Raleigh, and 1 in Greensboro) and 3 hospitals referred to as "remote' collection sites, which are >50 miles from the processing laboratory (Womack Army Medical Center in Ft. Bragg, NC, Carolinas Medical Center, Concord, NC; and Brigham and Women's Hospital, Boston, MA). See Table 1 for additional information.

At local hospitals, CCBB staff is responsible for obtaining informed consent from the birth mothers, pre-screening donors, and performing the ex-utero cord blood collections or assisting the MD/midwives in in-utero collections. Trained non-CCBB staff (MD/midwives) may perform in-utero collections from consented, pre-screened donors when the CCBB staff is not available (SOP CCBB-COL-021). At the hospital in Ft. Bragg, collections are performed by either the CCBB staff or trained MD/midwives and at the hospital in Boston, trained MD/midwives are responsible for all the collections.

Prior to obtaining consent, the birth mothers are pre-screened by trained hospital or CCBB staff and the pre-screening is documented (SOP CCBB-COL-002, and CCBB-COL-002 FRM 1). Potential donors with any of the following findings are excluded:

- Birth mother $\leq$18 years of age
- Pregnancy < 34 weeks gestation
- Multiple births
- Known congenital defects
- Positive skin test for tuberculosis without having received BCG vaccine
- High risk behaviors
- Any type of cancer in baby's mother, father or siblings

Note: Refer to the Donor Eligibility section for additional pre-screening exclusion criteria related to risks for communicable disease.

Birth mothers must sign a full informed consent either before or after the infant delivery. In some cases, a preliminary consent may be signed prior to the collection of cord blood. Collected cord blood units without a signed full consent will not be processed. In case of surrogate birth mothers, informed consent is obtained from both the biological and the birth mother. Prior to the collection of the cord blood unit and maternal specimens, the identity of the birth mother on the hospital label is verified against the mother's hospital wrist band, and the verification is documented (CCBB-COL-007 FRM 1, FRM2 and FRM3).

Collections at Non-fixed Sites (Kit Program)

Birth mothers interested in cord blood donation, obtain information regarding the program through NMDP or local public bank websites and contact the CCBB. The CCBB staff pre-screens mothers over the phone and documents the demographic information and the screening results. The pre-screening acceptability criteria are identical to those used at the fixed collection sites. If the donor meets the initial acceptability criteria, the pre-assembled collection kit is shipped to the birth mother around 36 weeks of gestation. The mother is instructed to maintain the kit at room temperature (CCBB-COL-014 FRM4) upon receipt of the kit. The collection kit includes the instructions for the mother and MD/midwife, collection supplies, consent forms, donor medical and family history questionnaires, maternal specimen tubes and the instructions for the cord blood collection, labeling, packaging and shipment of units to CCBB. A pre-activated data logger is included in the kit. The birth mother provides the collection kit to the labor and delivery staff who must verify the birth mother's identity (hospital generated labels verified against mother's hospital wrist band) and document the verification (CCBB-COL-016 FRM 2 and FRM3). The MD/midwife collects the cord blood following the provided instructions (same as the in-utero collection procedure performed at fixed collection sites). After completion of the collection, completed questionnaires, signed consent form, and the cord blood unit and the maternal specimens that are labeled with mother's hospital label, and completed questionnaires are shipped to CCBB via an overnight shipping service.

Reviewer comment: *The documents and forms submitted initially did not include any instructions for the MD/wife regarding the review of medical records. The Applicant submitted the revised forms on 8/10/12.*

COLLECTION TRAINING

Training of CCBB Collection Staff

The training program for the CCBB staff includes a 2 week introductory course at one of the collection sites (Rex Hospital, Raleigh, NC), observation of procedures, hands-on practice collections (units are not banked) and collections under the direct supervision by a senior staff. Each staff must successfully collect 3 consecutive units independently that have negative sterility results. In addition to the collection procedure, the CCBB staff are trained on the procedure for the donor pre-screening and consenting. The donor pre-screening criteria are also listed on a card which every collector carries with their ID badges. Annual staff competency is conducted and documented by a designated collection specialist or the Training Coordinator.

Training of Non-CCBB Collection Staff

Non-CCBB staff are trained by the Collection Site Coordinator on the *in-utero* collection procedure in vaginal or c-section deliveries. The Collection Site Coordinator reviews the "umbilical Cord Blood Collection Training for Public Donation" materials with the staff; and the staff must obtain a score of 100% on a quiz. The training module is provided either on-line or in printed format. Competency is assessed -(b)(4)- for collectors that performed (b)(4) units in the prior year (assessment is not performed for collectors performing (b)(4) collections). Collectors are considered competent if at least ----------(b)(4)----------

----------. If the minimum qualification criteria are not met, collectors are retrained (CCBB-TRN-002).

Training of MD/Midwives (Kit program)

The donor informs her MD/midwife of her intention to donate the cord blood prior to the time of delivery. The MD/midwife must complete an online training program through the NMDP website (www.marrow.org/ccbb). The training includes an overview of cord blood donation, description of materials provided in the collection kit, instructions for collection of maternal specimens, collection bag preparation, cleaning of the venipuncture site on the cord and collection of cord blood, labeling and preparing the container for shipping. Certification for the training requires a score of 100% on the on-line test (test may be retaken if score of 100% is not achieved). Training certification is sent via email to the MD/midwife and the CCBB staff. Units collected by physicians/midwives without a training certification are not banked for clinical use (SOP CCBB-COL-020).

Reviewer comment: *The training provided for the non-CCBB collection staff and the Kit Program is not as extensive as the training for the CCBB staff. However, basic training is provided, and the Applicant disqualifies units that don't meet the acceptability criteria; therefore, the training is acceptable.*

COLLECTION CONTROLS

CCBB has established the following controls for the collection procedure:

- Ex-utero collections are performed in a dedicated collection rooms at fixed sites. In-utero collections are performed in the delivery room.
- Identity of the birth mother on the hospital label is verified against mother's hospital wrist band the verification is documented before the collection of the cord blood unit and the maternal specimens.
- To minimize risk of contamination, cross contamination or mix-up: 1) collection staff wear appropriate gowning and protective equipment (for cesarean deliveries, CCBB staff follows the hospital operating room protocols for surgical scrubbing and gowning), 2) collection area at fixed sites is cleaned prior to each collection, 3) single use, sterile collection bag and antiseptic swabs are used for collections and the collection bag integrity is verified, 4) cord blood is collected only if the placenta is intact and has 3 vessels, 5) venipuncture site on the cord is cleaned with a povidone-iodine swab or Chloraprep applicator, 6) collected units are placed in individual biohazard bags which are placed in a small envelop that contains paperwork and ISBT barcodes , 7) shipping containers are cleaned.
- Unit collection is performed one at a time and the staff member collecting the unit is responsible for labeling the unit and all the associated paperwork.
- Relevant information such as type of delivery, infant weight, gender, and relevant physical and clinical observations, collection date, time and the collectors identity are documented (Fixed sites: CCBB-COL-008 FRM 1 and CCBB-COL-008 FRM 2; Kit program: CCBB-COL-016 FRM 2).

Cord Blood Unit Initial Qualification Criteria

For collections at fixed sites, a collection staff at each collection site determines the volume of the collected unit. Units that meet the initial volume qualification criteria ((b)(4) for minority donors and (b)(4) for Caucasian donors, excluding ----------(b)(4)----------) are labeled with a unique identification barcode label prior to temporary storage and transportation to the CCBB. For collections performed at non-fixed sites, the initial qualification of units is performed by the CCBB staff when the unit is received. In addition to the minimum volume requirement, the collected units must meet the following acceptability criteria prior to processing:

- <(b)(4) hours old
- Collection bag, maternal specimens, and forms labeled and packaged properly
- Signed consent
- For collections at non-fixed sites, collector's training certificate
- Pre-processing TNC (b)(4)

Reviewer comment: *In the initial submission, (b)(4) was listed as the minimum acceptable collection volume. However, currently the Applicant has different volume criteria for minority versus Caucasian donors. In the documents received on 8/10/12, the Applicant explains that the different volume criteria were established in order to maximize the number of units from minority donors in the inventory. This is acceptable because the units from the minority donors must still meet the pre-processing TNC requirement.*

Storage and Transportation

CCBB has two procedures for post-collection storage and transport of cord blood to the CCBB Processing Laboratory. The procedure used is based on the distance of the collection site to the CCBB. Remote collection sites are defined as greater than 50 miles from CCBB.

Transport from Local Collection Site

Storage and transport of CBU collected at local sites is performed according to CCBB-COL-009. CBUs are stored at room temperature in an ----------(b)(4)---------- shipper until the courier pick up for transport. Each labeled CBU is placed in a biohazard bag and placed inside a small envelop along with the completed Collection Form (CCBB-COL-008 FRM2) and additional ISBT labels. Data provided in the original BLA submission demonstrated that the (b)(4) shipper was validated to hold up to (b)(4) CBU for a period of 48 hrs between -(b)(4)-.

Transport personnel take CBUs out of the (b)(4) shipper and place into the local transport shipper. CBUs are transported from local collection sites to CCBB in the ----------(b)(4)---------- which can hold up to (b)(4) units. Transport coolers are inspected prior to use and decommissioned if damaged. CBUs are packed in the cooler in the following configuration: ----------(b)(4)----------. The Shipping Log (CCBB-COL-009 FRM1) is packed inside the cooler. With this packing configuration, these coolers were validated to maintain room temperature for up to --(b)(4)--.

Local Transport Validation Protocol: ----------

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

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

----------.

Results: The original BLA validation study report stated that the coolers were validated to maintain the temperature between (b)(4) for -(b)(4)-.

Note: *50% of the coolers failed to maintain the expected temperature for (b)(4).*

Reviewer Comments*: The original validation data was not acceptable. This issue was discussed with the Applicant during the Jan 6, 2012 t-con, and during the pre-market inspection (March 2 2012), after which the Applicant agreed to provide electronic data loggers in local transport coolers.*

Revalidation: In the June 1, 2012 amendment 008, the Applicant reported that they had re-validated the ---(b)(4)--- local shippers (Coolers) using the protocol described above.

Results: The Coolers maintained temperatures between --(b)(4)-- for up to (b)(4) when exposed to the simulated extreme temperatures described in the protocol. Thus, the revised validation study report supported a maximum (b)(4) transport time. The Applicant revised the transport procedure and will not pack electronic data loggers in local transport coolers.

During the validation study the data loggers indicated that the incubators were not always able to maintain the specified high temperature range -----(b)(4)----- when multiple coolers were inside; resulting in a protocol deviation. However, because the temperatures inside the incubators were always warmer than the record high North Carolina temperature this is acceptable.

Review Comment: *The Applicant demonstrated that the temperature range between --(b)(4)-- was maintained for only (b)(4), thus, limiting the validated transport time to (b)(4). Shipping Logs (CCBB-COL-009 FRM1) should be carefully reviewed during future inspections as temperature is a critical element for Ducord quality.*

Note: *The short timeframe for the validated transport cooler was a concern given that the maximum distance for local transport was ------(b)(4)------. These concerns were discussed with the Applicant on 7-17-12, and it was suggested that they add electronic data loggers to the coolers or the transport vehicles. The Applicant rejected these suggestions in their 7-26-12 response, stating that the local shippers are validated for (b)(4) and that any unit in transport for*

(b)(4) will not be acceptable for banking, including units coming in at ----(b)(4)----. The Applicant also revised SOP CCBB-LAB-017 to define local sites as those within 50 miles of CCBB. SOPs for receipt at CCBB (CCBB-LAB-017 and COL-016) were also revised on 8-10-12 to specifically state that units out of acceptable temperature and/or time ranges should be discarded and not banked.

Transport from Remote Collection Sites and Transport Validation

Up to (b)(4) CBUs can be transported from remote collection sites in insulated ----------(b)(4)---------- shippers (according to CCBB COL-012) which were validated to maintain temperature within --(b)(4)-- for up to 48 hours. Briefly, the CBU(s) are packed with ----------(b)(4)---------- to maintain the temperature of the cord blood during transport. Each unit is packed in its own biohazard bag with Collection Form. These shippers are also packed with an electronic data logger to track the temperature of the cord blood. Data for all shipments are downloaded (according to CCBB-LAB-049) and if a temperature is out of range, a deviation report is created and the unit is discarded according to SOP CCBB-LAB-005. Units are unpacked at CCBB according to CCBB-LAB-017, Receipt of CBU at the Processing Laboratory.

Reviewer comment: *Validation data was submitted with the original application for the insulated --------(b)(4)-------- shippers. The data indicates the shippers maintained the temperature between (b)(4) for up to 48 hours. In addition, electronic data loggers will be packed with each unit, and units outside the temperature range of (b)(4) will be excluded from banking and discarded.*

Transportation from non-fixed collection sites (Kit Program

Insulated shipping containers are used for transportation of collection supplies to the birth mother and the shipment of the collected units and maternal specimens from the hospitals to CCBB. A pre-activated electronic data logger is included in each shipper. The shipping containers include 1) silver foil Styrofoam lid, 2) flexible grey urethane plug, 3) two exogel temperature stabilizing panels, and 4) Cryopak pouch in a ziplock bag. Prior to each shipment, the shipper components are visually inspected for damage. Any shipper with visible damage is removed from service. The collected units must be maintained between (b)(4) during transportation (SOP CCBB-COL-019).

Reviewer comment: *The Kit Program Receipt of Cord Blood Units SOP (CCBB-COL-016) does not specify whether the cord units are acceptable for banking if the transportation temperature is outside the acceptable range. In the response letter received on 8/10/12, the Applicant clarified that SOP CCBB-COL-016 provides the instructions for the initial verification of the units received through the Kit Program and volume determination. If the unit meets the minimum volume requirement, then SOP CCBB-LAB-017 is followed to determine if all the receipt acceptance criteria which include the transportation temperature are met. The clarification is acceptable.*

Collection Bag and Supplies

Cord blood is collected in single use, sterile collection bags containing ----------(b)(4)----------. Lot number and expiration date of the collection bags, alcohol and Iodine swabs and Chloraprep are documented on the CBU Collection Form (CCBB-COL-008 FRM2). Please see Container Closure System section of this review for additional details.

For collections performed at the non-fixed sites, supplies included in the collection kit must have a minimum of 60 days to expiration from the date that the kit is shipped to the mother. A kit # is assigned to each collection kit per SOP CCBB-COL-014 and the number is documented on the Kit Program associated forms (CCBB-COL-016 FRM2 and FRM 3).

COLLECTION VALIDATION

The validation information submitted in the original application included a retrospective data analysis of contamination rates as well as comparison of the old collection bags (---(b)(4)---) to the collection bags that are currently in use (---(b)(4)---). At the request of the review team, Applicant performed a prospective validation which included all the manufacturing steps from collection of cord blood units to post-thaw (Validation Report Protocol No. 2012-011 P, submitted on 6/1/12). The sections of the validation related to the cord blood collection and the transportation of units from the collection facilities to the processing laboratory are reviewed in this section.

Protocol description:

The validation included minimum of (b)(4) consecutive cord blood units collected from Caucasian donor infants at 3 collection sites. The Applicant explains that units from non-Caucasian donors and also units with (b)(4) volume were not used in the validation in order to maximize banking of units from donors with rare HLA types and those with higher volume and cell dose. The collection and transportation was performed according to the established SOPs.

Reviewer comment: *Because the procedures for collection and transportation of units are the same for all donors, the Applicant's reason for excluding units collected from minority donors from the validation plan is acceptable.*

Acceptance criteria:

- Collection volume: (b)(4) (Caucasian donors)
- Transport temperature: (b)(4)
- Pre-processing TNC: --(b)(4)--
- Pre-processing sterility culture results: No growth

Validation outcome:

Total of (b)(4) collected units were evaluated for this validation. Upon receipt of the collected units in the laboratory, the collection bag integrity and the associated paperwork were verified and all

found to be acceptable per defined SOPs. All the collected units met the acceptance criteria with respect to volume, transport temperature, pre-processing TNC and sterility culture results.

***Note**: In the validation summary report, the acceptable transport temperature was changed to (b)(4). The Applicant explains that the modification was done in order to be stricter and comply with current SOPs.*

***Reviewer comments:** The modification in the temperature range is acceptable because all the (b)(4) collected units for this validation were transported within -(b)(4)-. The validation did not include units received through the Kit Program. However, the same procedures are used for collection of units through this Program. Furthermore, any unit that does not meet the banking acceptance criteria is discarded. Therefore, the validation is acceptable.*

REAGENTS USED IN MANUFACTURE

Citrate Phosphate Dextrose (CPD) (----------(b)(4)----------) is an anti-coagulant supplied --------(b)(4)----------.

Hespan
Hespan (--------(b)(4)---------) is used as a sedimentation agent to sediment red blood cells and neutrophils in cord blood in order to separate the mononuclear cells. Hespan is an FDA approved reagent (NDA BN070012). It is supplied as 6% hydroxyethylstarch in 0.9% sodium chloride in 500 ml volumes. ----------(b)(4)----------.
Aseptic assessing of the Hespan bag was verified during process validation.

DMSO/Dextran 40
The cryoprotectant used in manufacturing is a mixture of DMSO and Dextran 40 (--(b)(4)--DMSO and (b)(4) Dextran 40). The reagent is procured as ----------(b)(4)---------- from (b)(4) suppliers (----------(b)(4)----------). The Applicant claims that although their priority is the use of the ----------(b)(4)---------- is procured for back-up purposes.

The lot number and expiration date of the reagent are recorded as part of the batch record. As part of reagent qualification, each lot is tested for sterility (---------(b)(4)-------- per lot) prior to use.

The Applicant contracted ----------(b)(4)---------- to perform identity and concentration testing on the reagent from ----------(b)(4)----------. The ----------(b)(4)---------- was used in this analysis and the test report submitted confirmed the identity of the cryopreservation solution. The results of (b)(4) analysis also confirmed the information contained in the Certificate of Analysis (COA) for DMSO from ----(b)(4)----.

Note: *COAs for Hespan and DMSO/Dextran 40 were submitted upon request.*

CORD BLOOD PROCESSING

Overview

A single method of processing cord blood is used under this BLA, an ----------(b)(4)---------- (See Table 18 Containers and closures).

Receipt of Cord Blood Unit in Processing Lab

(SOP: CCBB-LAB-017)

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

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

----------**(b)(4)**----------**.**

Cord Blood Processing Using ---(b)(4)--- Method

The collected cord blood is volume reduced by depleting the red blood cells and plasma before cryopreservation. The SOP CCBB-LAB-022, entitled 'CBU Processing', is followed for cord blood processing and the QC worksheet, CBU Processing Form FRM1, is used to document the processing steps.

The --------(b)(4)--------- is used to process cord blood. Cord blood volumes of ----------(b)(4)---------- (volumes do not include anticoagulant) qualify for processing --------(b)(4)-------.

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

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

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

----------.

Processing Details

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

3 pages redacted (b)(4)

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

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

----------.

__Note__: A cross-reference of authorization for the Thermogenesis master file (b)(4), was submitted for the Thermogenesis BioArchive long-term storage system.

CORD BLOOD PROCESSING VALIDATION

Protocol Number 2012-011-P was followed for the process validation study to demonstrate a controlled collection, processing, cryopreservation, and thawing of HPC, Cord Bloods. The validation results were reported.

Description of Protocol

The protocol (Protocol 2012-011-P) outlined the procedures and acceptance criteria for the validation. Cord blood units (CBUs) were collected over a 4 day period, processed per SOPs as previously described (receipt, volume reduced with the -----(b)(4)------, cryopreserved and stored).

A total of (b)(4) consecutive cord blood units were processed for this validation study. The units were collected from 3 collection sites, processed, and tested according to the appropriate current SOP. CBUs from non-Caucasian donors and CBUs with (b)(4) volumes were not used for the validation because of rare HLA-types in minority populations (non-Caucasian donors) and higher cell doses delivered by larger cord blood volumes.

Collected CBUs were transported to the processing facility at -----(b)(4)-----; electronic temperature data loggers were included in the transporters to record the transit temperatures. The temperature data from the data loggers was downloaded prior to processing to ensure that the ----(b)(4)---- range was maintained during transport.

Post-Thaw validation

To determine whether frozen HPC, Cord Blood units met the post-thaw criteria, ---------(b)(4)---------- cryopreserved HPC, Cord Blood units were thawed (--(b)(4)--) according to the Procedure for Thawing Umbilical Cord Blood Units Frozen in Two Compartment Bags using Dextran 40-Albumin Solution and tested as outlined in Table 5 below.

Acceptance criteria for the post-thaw validation study

The applicant proposed setting the acceptance criteria for the post thaw validation at (b)(4), meaning that (b)(4) of the units used in the thaw/wash validation study must meet all pre-set specification for the validation to be acceptable. Units that do not meet pre-cryopreservation specifications are at not banked. The applicant justified their acceptance criteria based on an analysis of historical data for thousands of units thawed for transplant at Duke. This analysis demonstrated that approximately (b)(4) of thawed units did not meet all specifications upon thaw. The Applicant did not find an apparent pattern or trend for these failures and proposed that the failures could be attributed to the inherent variability of HPC, Cord Blood due to biological differences in the donor.

Reviewer comment: *The (b)(4) acceptance criterion is conservative as the actual data indicated (b)(4) pass rate. In addition, the applicant is analyzing specifications that are not required by the FDA guidance document for Licensed Cord Blood (i.e. % recovery of CD34+ is not specified but absolute number of CD34+ cells is specified).*

***Sampling for testing*:**
A sample (b)(4) of the in-coming collected cord blood was taken for sterility testing to rule out contamination resulting from processing; (b)(4) each was inoculated per vial (aerobic and anaerobic vials). Pre-cryopreservation sampling was described above.

------(b)(4)------- processed HPC, Cord blood were thawed and washed in accordance with the procedures sent out with HPC, Cord Blood shipments to the transplant centers. For this evaluation, (b)(4) HPC, Cord Blood were thawed per day after (b)(4) of storage in liquid nitrogen and analyzed. A (b)(4) sample was removed from the final washed product ((b)(4) infusion bag) using a sterile 3 mL syringe. -(b)(4)- used for cell count via ----------(b)(4)---------- and (b)(4) used for --(b)(4)-- CD34+ enumeration via flow cytometry. (b)(4) samples were removed from the wastebag (supernatant) and split into -------(b)(4)------ bottles for sterility testing.

As part of this validation, a total of (b)(4) HPC, Cord Bloods were checked for volume using a syringe regardless of whether these units met the established post-processing weight criterion. This was done in addition to post-processing weight check that is routinely performed for all processed HPC, Cord Blood.

A sample of Hespan (b)(4) was also assessed for sterility at the beginning and end of each day to assure that aseptic technique was used during the multiple entries into the Hespan container

during the day. ---(b)(4)--- was inoculated per sterility vial for aerobic and anaerobic sterility cultures.

Process Validation Specifications

The criteria used in the process validation are specified in Table 5 below.

TABLE 5: PROCESS VALIDATION SPECIFICATIONS

Test	***Test Sample***	***Specification***
Minimum Collection Volume	Weight of the Collection bag post collection	(b)(4)
Transport Temperature from Collection site Processing laboratory	Na/ data provided by data logger in local transport coolers	(b)(4)
Pre-qualification Total Nucleated Cell Count (TNCC)	Sample of Whole Cord Blood (including CPD) from Collection Bag	---(b)(4)--- cells
Mass of Post Processed HPC, Cord Blood **Product Bag***	n/a; use cryobag on designated scale	-----(b)(4)-----
Viability	Sample from Post-Processed HPC, Cord Blood Cryobag	(b)(4)
Post-Processing Total Nucleated Cell Count (TNCC)	Diluted Sample from Post-Processed HPC, Cord Blood Cryobag	$\geq 9.0 \times 10^8$ cells
--------**(b)(4)**--------	----------(b)(4)----------	(b)(4)
Viable $CD34^+$ Cells	Sample from Post-Processed HPC, Cord Blood Cryobag prior to addition of DMSO/Dextran 40	$\geq 1.25 \times 10^6$ cells
Sterility	(b)(4) post-processed plasma and (b)(4) post-processed red blood cells	No growth (negative)
(b)(4)	----------(b)(4)----------	(b)(4)
Freezing Curve	n/a; BioArchive print out accessible	------(b)(4)----------
Testing of the Final Product Bag Post-wash		
Post-Thaw Recovery of Viable TNCC**	From sample of cells after thawing cryobag	(b)(4)
Viability	From sample of cells after thawing cryobag	≥85%
Sterility	From sample of cells after thawing cryobag (---(b)(4)---)	No Growth (negative)

Test	*Test Sample*	*Specification*
CD34+	From sample of cells after thawing cryobag (---(b)(4)---)	----(b)(4)----
(b)(4)	----------(b)(4)---------- ----------	----(b)(4)----

*Because it is part of the process, the validation must ensure that at least some of the post-processing HPC, Cord Blood cryobags are also tested for volume using a syringe in a BSC. For this testing (b)(4) cryobags were checked regardless of the results from the weight check.
**Thawing will take place in the Duke Stem Cell Laboratory (STL) according to the recommended CCBB procedure that is sent out with each product to a transplant center (CCBB-DIST-028). Products must be cryopreserved for a ----------(b)(4)---------- prior to thawing. Post-thaw tests were performed per SOP in the Duke STL for product post thaw.

Note: *The temperature criterion for transporting collected CBUs to the processing facility was changed from (b)(4) (as indicated in Table 5) to (b)(4) after the validation. The Applicant explained that this range reflected the operating conditions better.*

Note: *The validation protocol stated that thawing process would be performed according to CCBB-DIST-028. However, the applicant revised the protocol description in amendment 019 to state that the protocol used for the thaw/wash validation study was STCL-SOP-028, which is the protocol used by the Duke Stem Cell Laboratory to ----(b)(4)---- thaw HPC, Cord Blood units prior to transplant. SOP CCBB-DIST-028 is a slightly modified version of STCL-SOP-028. The two procedures are identical, except CCBB-DIST-028 contains instructions for emergency product recovery; which does not affect the validation procedure.*

Results: Pre- and Post-Processing

The transport temperatures for the collected CBUs are within the specified range of --------(b)(4)-----. Only units received within (b)(4) of pick up at collection site are acceptable for banking according to revised SOP CCBB-LAB-017.

The results of the collected CBU volumes, the pre-processing sterility testing on the starting CBU, and post-processing volume check demonstrated that all the CBU used in the validation met the minimum criterion of (b)(4). A post-processing volume verification using a syringe was performed on (b)(4) HPC, Cord Blood and volumes obtained ranging from ---(b)(4)-- ml met the acceptance criterion. The sterility testing on the starting CBUs samples were all negative.

The test results on the HPC, Cord Blood characterization before cryopreservation and the freezing curve transition, as well as the post-processing sterility test results are summarized in Table 6. All established criteria were met in the validation.

Negative sterility test results were obtained for the daily testing of Hespan reagent over the course of four days.

TABLE 6: VALIDATION TEST RESULTS: POST PROCESSING AND CRYOPRESERVATION

(b)(4)

(b)(4)

Validation Results for the Post-thaw HPC, Cord Blood

Table 7 lists the results of post-thaw characterization of the HPC, Cord Blood (includes TNC, CD34+, and CD34 recovery. All the results met the acceptance criteria for the attributes characterized, except for CD34+ cell recovery for one of the (b)(4) cord blood units used in the validation. A (b)(4) recovery was obtained instead of the established criterion of (b)(4), but the absolute CD34+ cell numbers for this unit met the acceptance criterion.

TABLE 7: VALIDATION TEST RESULTS: POST-THAW ANALYSIS DATA

(b)(4)

Reviewer Comment*: While, one unit failed one parameter of the post thaw validation study, the process validation results are adequate. This conclusion was made based on an evaluation of the*

validation protocol and the supporting data submitted in the BLA. Briefly, the validation study included analyses of product quality parameters that were not required by the Cord Blood Licensure guidance. In particular, the applicant evaluated % CD34 recovery post-thaw, which is not required by the guidance. The guidance states that HPC, Cord Blood must have ≥1.25x10^6 CD34+ cells, which the unit that failed % CD34 recover in the post-thaw validation study, did achieve. Thus, while one unit did fail to meet specification for CD34 cell recovery, it met criteria for absolute number of CD34+ necessary for product release. Thus, because the CD34+ cell number requirement was met the validation is considered acceptable.

In addition, the applicant met the pre- set acceptance criterion of "meeting established criteria (b)(4) of the time." The (b)(4) pass criterion was set based on a conservative assessment of the applicant's historical experience with analyzing post-thaw HPC, Cord Blood. The data for the historical analysis was collected from HPC, Cord Blood units that were thawed and washed for transplant at Duke using the same procedures used in the validation study. Briefly, the original BLA contained post-thaw data analyses for thousands of HPC, Cord Blood units that were thawed for transplant at Duke. This data indicated that approximately (b)(4) of units thawed do not meet specification for TNC recovery. However, this analysis contained confounding data (i.e. pre-cryopreservation data supplied by Cord Blood banks other than Duke, see Stability section of this review). Thus, the applicant also submitted an analysis of a subset of that data for hundreds of units processed and thawed at Duke (amendment 013). This data indicated that nearly (b)(4) of units pass specifications. Thus, while the criteria set by Duke for acceptance of the post-thaw validation study was conservative, they met their pre-set validation criteria, and the validation is acceptable.

***Note:** Please see data analysis in the Stability section of this review for more details.*

SHIPPING AND SHIPPING VALIDATION

Cord Blood shipping from collection site to CCBB is discussed above under Collection Validation.

HPC, Cord Blood shipping to transplant center: The validation data for the dry shippers was provided in the original BLA in Section 3.2.P.3.2.1. Briefly, once cryopreserved, Ducord must remain at ≤-150°C throughout shipment to the transplant facility. Dry shippers are used for the shipping of Ducord at ≤ -150°C. The shippers have been validated to maintain temperature at ≤ -150°C for (b)(4). The typical shipping time is 48 hours. An electronic data logger accompanies each shipment of Ducord to the transplant center.

Verification of shipping temperature: When a Dry Shipper is returned to CCBB, the information from the electronic data logger is downloaded, printed, and filed according to SOP. The expected temperature range is from ≤-150°C to (b)(4). Any temperature issues are immediately brought to the attention of the Operational Manager of the CCBB Processing Laboratory. If a temperature issue is confirmed, the NMDP is also notified. The temperature data and NMDP Form 600 for each HPC, Cord Blood product are reviewed and added to the CCBB

manufacturing file for that Ducord product. The Ducord file is submitted to the laboratory supervisor for review and signature, which is then returned to the Operations Manager for filing.

Reviewer comment: *The data was acceptable to support validation as all specifications were met.*

THAWING AND WASH PROCEDURE: PREPARATION FOR INFUSION

Instructions for preparing HPC, Cord Blood for infusion must accompany each HPC, Cord Blood sent to transplant centers. While each transplant center may follow their own procedures for preparing a HPC, Cord Blood units for transplant, following the instructions from CCBB will result in the highest quality Ducord product being infused. The thawing procedure recommended for Ducord was validated to demonstrate proficiency and control of the thaw/wash process.

The **thawing/dilution/wash** process is described in CCBB-DIST-028, *Procedure for Thawing Umbilical Cord Blood Units Frozen in Two Compartment Bags using Dextran 40-Albumin Solution.* This procedure was previously sent with all HPC, Cord Blood units shipped from CCBB to transplant centers.

Note: *At the request of the review team a more general version of the SOP CCBB-DIST-028, which does not contain references to other CCBB SOPs and FORMS, was developed for inclusion with the Package Insert that will accompany each unit of Ducord shipped to transplant centers. The review team also recommended additional formatting changes which were provided with the final version of the Instructions for Preparation for Infusion.*

Reviewer Comment: *Following multiple review and discussions with the applicant, Instructions were developed that were sufficiently clear and acceptable. The Instructions for Preparation for Infusion will be appended to the PI that accompanies each Ducord product.*

Thawing: The applicant emphasized that aseptic technique should be used and all open manipulations should be performed in the biosafety cabinet (BSC). The thaw/dilution/wash process involves many steps that should be performed in a timely manner for best product recovery. In addition, all materials and solutions should be assembled prior to thawing Ducord. The product's ISBT 128 label should be verified when the metal canister containing Ducord is removed from cryostorage. Attached segments should be removed and labeled with patient ID, and stored in liquid nitrogen. Ducord should be wiped gently with 70% alcohol, placed in a sterile ziplock bag and rapidly thawed to a slushy consistency in a 37°C water bath.

Dilution: A cell wash/infusion (transplant) bag set (e.g. bag includes necessary tubing, ports and connections) labeled with unique identifiers should be attached to the cryobag and cold (2-8°C) thawing solution (10% Dextran 40 and 4.2% human albumin) should be slowly allowed to drain into the cryobag until both cryobag compartments bulge. After gently mixing by hand the cryobag contents should be drained into the infusion bag and mixed with the remaining thawing solution. The instructions recommend that the cryobag be rinsed two times to collect remaining cells (cells suspension #1). Cells should be kept at 2-8ºC using ice packs.

Washing: The infusion bag containing cells (cells suspension #1) should be gently spun (1800 rpm for 20 min) in specially designed buckets to remove DMSO, free hemoglobin, and the majority of cell debris. The majority of the supernatant should be removed to an attached transfer bag using a platelet expresser and centrifuged to collect as many cells (cell suspension #2) as possible.

Infusion preparation: Cells can be prepared for infusion using either a BAG (adult) or SYRINGE (pediatric) method depending on physician designation and patient weight. Details for how to prepare the cells for each method are included in the Thawing instructions. Briefly, a QC sample is obtained (0.9 mL for viable cell recovery) from the infusion bag to determine cell number. For the Bag method, the final prepared infusion bag should be labeled with a Demand 128 label or equivalent and a tie tag (see Labeling section of this review) containing recipient and donor information. The infusion bag should be sterile docked to a 150 ml transfer bag containing 20-100 mL sterile saline solution, which will be used to rinse the infusion bag after the infusion procedure. For the Syringe method, the cells should be filtered through a hemoset filter (not leukoreduction filter) and drawn into a 60 mL syringe. The Syringe barrel should be labeled with tie tag containing recipient and donor information. Each transplant center should complete transplant data forms to record cell recovery data, all labels must be verified and the product is then transported to the transplant unit in a validated transport container.

Quality Control Tests: Transplant centers are advised to perform the quality control tests and provide results to CCBB and CIBMTR. Recommended tests include: Cell counts in set volume (to determine dose), viability, CD34+ cell count, progenitor cell assay for CFU-GM, GEMM, and BFU-E on infusion-ready product, and sterility tests on supernatant from the final wash, and if requested, RFLP on approximately $1x10^6$ cells (0.2 mL) from infusion-ready product.

THAWING AND WASH PROCEDURE VALIDATION

The validation data included in the original submission, which included % TNCC recovery data obtained pre-cryopreservation (pre-cryo) and post-thaw (after washing) data for HPC, Cord Blood units that were transplanted at Duke, was not acceptable. Pre-cryo data was provided to Duke by the individual cord blood banks that supplied HPC, Cord Blood units for transplantation at Duke. Post-thaw data was obtained from tests performed by the Duke Stem Cell Laboratory (SCL) using samples obtained after thawing and washing. Duke reported a median post-thaw TNCC recovery for all units transplanted as 81.1%.

Review Comment: *The validation data submitted in the original submission was not acceptable because the study was a retrospective analysis of historical data collected from pre and post thaw HPC, Cord Blood units that were not tested using the same methods or by the same laboratories. CCBB could not demonstrate adequate control of the methods used for this analysis and they did not submit the post-thaw viability data. A prospective study of the thaw/wash process validation was requested during the Jan 6, 2012 t-con.*

Revised Thaw/Wash Validation Protocol: A prospective thaw and wash process validation study was performed as part of the Ducord process validation protocol described previously in

this review (submitted in amendment 008, revised in amendments 017 and 019. Briefly, 4 units of the 11 units cryopreserved during process validation were to be thawed and processed for infusion (according to CCBB-DIST-028), sampled for analysis as summarized in Table 5 above. Samples were collected post dilution and wash (per Applicant 8-10-12 t-con). The validation was acceptable (see Process Validation section of this review).

Reviewer Comment: *As noted in the process validation section the thaw wash protocol used in the validation study was revised in amendment 019 to state that STCL-SOP-028 was used for the validation procedure not CCBB-DIST-028. This is acceptable, because STCL-SOP-028 and CCB-DIST-028 are essentially the same procedure.*

Note: *Stability of Ducord following preparation for infusion is reviewed in the Stability section.*

EMERGENCY PRODUCT RECOVERY

The original submission did not contain a procedure for emergency product recovery. The Applicant was requested to provide a product recovery plan in the filing letter. The Applicant submitted an updated SOP for thawing, dilution and washing of product for infusion at the transplant site that included additional directives for Emergency product recovery (SOP CCBB-DIST-028 version 02) in Amendment 005. These procedures were revised in the Amendment 008 submitted on June 1, 2012. Briefly, the revised SOP includes instructions to handle each cryobag with extreme caution when removing product from the liquid nitrogen, metal cassette, and protective overwrap, wipe the unit with alcohol prior to thawing, and thawing the unit in sealed sterile overwrap bag to maximize the opportunity to recover the cells. If the container is compromised they recommend performing additional sterility testing (Gram stain prior to administration), notifying CCBB and the transplant physician and the local laboratory director immediately. The transplant physician (or designee) determines if they want to use the Ducord product or discard it. If the decision is made to infuse Ducord, the Emergency Product Recovery recommends using a long blunt needle (a sterile spinal needle with trochar removed) attached to a sterile 60 ml syringe to aspirate product and inject into a sterile transfer bag and proceeding with recommended wash procedure. CCBB recommends that a sample be tested for sterility after the final wash process and that the clinical team be alerted that the product was violated and could potentially be contaminated with bacteria. The applicant recommends that the clinical team be instructed to cover the patient with broad spectrum antibiotics until it is known that the cultures from the product are negative. If possible, CCBB requests that the ruptured bag be saved and returned to CCBB for an investigation.

Reviewer Comment*: These instructions are acceptable.*

QUALITY CONTROL TESTING

In process controls

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

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DUCORD LOT RELEASE TESTING

SAFETY TESTING

Maternal Infectious Disease Testing

Please see Donor Eligibility section of this review for details. Briefly, maternal infectious disease testing is performed on samples of maternal peripheral blood for each Ducord lot. The results from each of the Maternal Infectious Disease tests must be negative (except for the CMV antibody test, which is discussed below).

Cytomegalovirus (CMV) Testing

The cytomegalovirus (CMV) antibody screen is performed using FDA approved tests (----------(b)(4)----------) on a sample of maternal peripheral blood for each collected CBU. CMV screening results that are negative require no further testing. If the CMV antibody screen is positive, a ---(b)(4)--- test is performed to determine if a Ducord product contains virus DNA.

Sample: The sample for the CMV (b)(4) assay is a ----(b)(4)---- removed from the --(b)(4)-- fraction obtained during Ducord processing. ----------(b)(4)----------.

Method: ----------
----------(b)(4)----------

----------.

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

---.

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

---.

Specification
Ducord units with negative CMV (b)(4) results are acceptable for release. Negative samples are those with no copies of CMV DNA detected. Ducord units which test positive -------(b)(4)------ or indeterminate/low positive --------(b)(4)------ for the virus are excluded from banking and are not placed into distribution. Clinical CMV infection is generally associated with copy numbers in the range of 50,000-2,000,000 copies/mL of the CMV virus in whole blood.

Note: *According to the Applicant, (b)(4) samples contain approximate 10-fold less DNA than whole blood samples.*

CMV (b)(4) Assay Validation

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

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

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CMV -(b)(4)- assay Validation part 2

The Applicant followed the validation protocol (2012-003-A). The CMV assay is performed as a limits tests and as such the analytical performance parameters considered were Specificity and Limit of Detection (ICH Guideline Q2 (Rl), Validation of Analytical Procedures). The equipment and reagents used to perform the procedure were accurately represented in the protocol.

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

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Reviewer comment: *The Applicant did not validate specificity, but inferred it from the reagents used. However, this is acceptable given that internal positive and negative controls for specificity are included each time the assay is performed. Additional controls include: CMV* *(b)(4)*

is the only (b)(4) assay performed in the CCBB laboratory and the (b)(4) area is segregated from the rest of the laboratory, thus, reducing the risk of cross-contamination.

Limit of detection (LOD): The limit of detection was assigned at the number of copies where all three replicates of a particular concentration tested give a positive signal in all three -(b)(4)- samples. Thus, for a particular DNA concentration, nine (9) (b)(4) samples must flag as positive in the assay.

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

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

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

----------.

--(b)(4)--:

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

----------**(B)(4)**----------

(B)(4)

Reviewer comments: *Clarifications of the assay and data were requested of the Applicant during the 7-17-12 t-con. These were addressed by the Applicant on 7-26-12. Briefly, the Applicant was requested to comment on the high degree of variability for the replicates prepared from the same DNA samples (i.e. a-c). The Applicant stated that variability could be due to DNA recovery, but they didn't see this as a safety concern since the LOD is well above the copy number for clinical infection (range of 50,000-2, 000,000 copies/mL of the CMV virus in whole blood).*

Note: *The original validation protocol did not specify the degree of variability they were willing to accept prior to the validation exercise. After analysis of data they stated that they were willing to accept a relatively high level of variability (CV (b)(4)) because the acceptable level of variability depends on the potential consequences of a false negative result. They stated that a LOD of (b)(4) copies is extremely conservative given clinically relevant copy number for CMV. Variability data provided in amendment 012 is shown in Table 9.*

----------**(B)(4)**----------

(b)(4)

Reviewer Comment: *The CMV (b)(4) assay is a limits test, and the limit of detection demonstrated in the validation exercise is well below the clinically relevant CMV copy number, thus, this validation is acceptable for its intended purpose. Moreover, Ducord will not be released if CMV DNA is detected at any level. The variability that the applicant finds acceptable makes the assay a semi-quantitative assay, which is acceptable for a limits test. In addition, because the CMV DNA (b)(4) test is not a required donor eligibility test for risks of relevant communicable diseases or disease agents (RCDAD) the higher variability in the assay is tolerable.*

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

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Hemoglobinopathy Testing

Hemoglobinopathy Reports are obtained in accordance with SOP CCBB-COL-029 for each qualifying HPC, Cord blood from the state laboratory (where the infant was born). Most states send specimens for newborn screening to state laboratories. States currently supplying these results to the CCBB include North Carolina and Massachusetts.

North Carolina: The delivering hospital sends newborn screening specimens to the NC State Testing Laboratory (NCSTL CLIA #34D0692393) as part of normal procedures. The CCBB staff does not initiate the transmission of these samples. The NCSTL has authorized the CCBB to directly access the NCSTL's database and print hemoglobinopathy reports for infants whose cord blood was collected in the state of North Carolina. Using the demographic information on the Volunteer Cord Blood Donor Identification Form (VCBDIF) in the confidential file folder, the designated CCBB staff member obtains the hemoglobinopathy report from the NCSTL database. Hemoglobinopathy screening in North Carolina is performed using ----------(b)(4)----------.

Massachusetts: (CLIA # 22D0935548): Boston collection site personnel contact the staff of the New England Newborn Screening Program who provide a paper copy of the hemoglobinopathy testing result to the staff at the Brigham and Women's Hospital collection team. The staff at BWH sends test results for each unit collected to the CCBB in a confidential packet via Federal Express. Hemoglobinopathy screening in Massachusetts is performed using ----------(b)(4)----------.

Kit Program: For cord blood collected through the "Kit Program," hemoglobinopathy results are obtained by the CCBB clinical coordinator from the donor's pediatrician. The pediatrician receives the results from the relevant state newborn screening program. The mother of the newborn agrees, when signing the informed consent for cord blood donation, to allow the results of the newborn screening panel to be sent to the CCBB. Hemoglobinopathy screening test method in these cases will depend on the individual state program.

Specification: No disqualifying abnormal homozygous hemoglobin or disqualifying double heterozygous hemoglobins may be present in a qualifying product. Heterozygous hemoglobin traits will be listed in the comments section of the release form to inform the transplant physician but do not disqualify the product.

Method Validation: The Applicant stated that all method validations are performed by the North Carolina State Laboratory of Public Health (CLIA #34D0692393). Some cord blood units are collected from fixed, contract collection sites in other states (currently only Massachusetts), and hemoglobinopathy results for these cord blood units are also obtained through the relevant

state-appointed laboratory (Massachusetts Screening Laboratory, CLIA # 22D0935548). These laboratories are CLIA certified to perform these assays, and as such FDA does not require additional test method validation.

Reviewer Comment: *This process is satisfactory given that the testing laboratories are CLIA certified and there are SOPs in place to ensure that test results are properly tracked to individual cord blood donors.*

Sterility Testing and Method Validation

The tests for microbial contamination are performed on a sample of the plasma and red blood cells waste fractions from each processed CBU using the ---(b)(4)--- system. The culture results must be negative (no growth). Any CBUs that obtain a positive result in this sterility test are disposed of per standard procedures.

Sterility test procedure and lot-release specification:

1. ----------(b)(4)----------.
2. ----------(b)(4)----------

   ----------***(b)(4)***----------.
3. ----------(b)(4)----------.
4. ----------(b)(4)----------.
5. ----------(b)(4)----------.

Written procedures for the sterility test:

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

Reviewer Comments:

1. *----------(b)(4)----------.*
2. *The Applicant has established and will follow SOPs for the sterility test. The information submitted on the composition of the culture media and incubation*

conditions are adequate and acceptable – complies with 21 CFR § 610.12 (c)(1)(i)(A) and 21 CFR § 610.12 (c)(1)(i)(C).

Sample used for the sterility test:

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

2 pages redacted (b)(4)

1. *----------(b)(4)----------.*
2. *----------(b)(4)----------.*
3. *----------(b)(4)----------.*

Reviewer Comments on Other Issues:

1. There will be no repeat test for the sterility assay under any circumstances – *therefore 21 CFR § 610.12 (f) is not applicable.*
2. *Due to inherent limitation of the sampling method used for the sterility test (especially under low bioburden conditions) and the fact that the processed cord blood final product is not suitable for terminal sterilization, the Ducord product should not be labeled as sterile.*

Consideration of the inhibitory effect of residual antibiotic

The BLA does not exclude donor mothers on perinatal antibiotic prophylaxis, a treatment recommended in CDC guidelines for the prevention of neonatal sepsis caused by Group B Streptococcus (MMWR 2010 59:RR-10). The applicant provided information that up to 55% of deliveries involve perinatal prophylactic treatment with penicillin or clindamycin or cefazolin. The mothers are treated either few weeks before delivery, or as in most cases, during labor and delivery (intrapartum).

The use of intrapartum antibiotics raises the question about the potential for residual antibiotics in the product. A survey of the available literature suggests that almost all antibiotics

administered to the mother cross the placenta to reach the fetal blood (Ginsburg J, Annu. Rev. Pharmacol. 1971.11:387-408 and Pacifici GM, Int. J. Clin. Pharmacol. Ther. 2006 Feb;44(2):57-63). Thus, the test samples derived from the cord blood units isolated from mothers on intrapartum prophylactic antibiotic have the potential to inhibit the sterility test and give false negative results, if organisms are present and not killed by the antibiotics, but inhibited from growth in the culture media.

We considered the following points to reach the recommendation below:

Antibiotic dose: For the prevention of Group B streptococcal sepsis in newborns the CDC recommends the following intrapartum antibiotic regimens (MMWR 2010 59:RR-10).

- "Penicillin G, 5 million units IV initial dose, then 2.5-3.0 million units every 4 hours until delivery"
- "Ampicillin 2 gm IV initial dose, then 1 gm IV every 4 hours until delivery"
- "Cefazolin 2 gm IV initial dose, then 1 gm IV every 8 hours until delivery"

For patients with the history of allergic reactions to β-lactam antibiotics

- "Vancomycin 1 gm IV every 12 hours until delivery"
- "Clindamycin 900 mg IV every 8 hours until delivery"

Reviewer Comments: *The recommended doses are equivalent to the standard IV doses and would maintain the maternal serum antibiotic levels at or well above the trough level for the duration of the prophylactic treatment.*

Antibiotic Transfer: In general the placental antibiotic transfer occurs rapidly, within 90 minutes, resulting in bacteriostatic levels of antibiotics in the fetus (Ginsburg J, Annu. Rev. Pharmacol. 1971.11:387-408). Depending on the class of antibiotics used three types of placental transfer could occur. *Complete transfer* – concentrations of antibiotics are equal in maternal and fetal blood; *Incomplete transfer* – concentration of antibiotics in the fetal blood is lower than the maternal blood; *Exceeding transfer* – concentration of antibiotics in the fetal blood is higher than the maternal blood (Pacifici GM, Int. J. Clin. Pharmacol. Ther. 2006 Feb;44(2):57-63). Data suggest that Ampicillin is transferred completely while the Vancomycin (76%) and Clindamycin (44%) are transferred incompletely (Pacifici GM, Int. J. Clin. Pharmacol. Ther. 2006 Feb;44(2):57-63).

Reviewer Comments: *Based on the CDC recommended dose, timing of administration and the placental rate of transfer it is highly possible to have bacteriostatic levels of antibiotics in the cord blood isolated from a mother on intrapartum prophylaxis. The residual antibiotics could compromise the sterility test of the product. The residual β-lactam antibiotics could also induce an allergic reaction in a sensitive Ducord recipient.*

Dilution factor: For this BLA the cord blood is mixed with an anticoagulant and Hespan before processing resulting in about a (b)(4) fold dilution of the original sample.

Reviewer Comments: *This (b)(4) fold dilution may not be enough to reduce the inhibitory effect of the cord blood with antibiotic present at peak therapeutic serum level.*

Exclusion criterion: In this BLA, the infant and the mother are followed up for peri- or post-partum infection and sepsis and either of these conditions excludes the cord blood from banking.

Reviewer Comments: *This exclusion criterion is not sufficient as it does not consider the possible environmental contaminants present during the collection and processing.*

Assay Validation: The sterility test validation in this BLA was not designed to assess the potential effect of the presence of residual antibiotics because the cord blood samples used in the validation were obtained exclusively from non-febrile mothers lacking any perinatal antibiotic treatment. Additionally, the ---------(b)(4)---------- media used by the applicant do not contain components capable of neutralizing antibiotics.

The review team considered ways the Applicant might alter the sterility test to resolve the theoretical concern. There are several options –

- Add sufficient quantities of β-lactamase (if β-lactam antibiotics are present) as per USP <71> to the culture bottles
- Include a membrane filtration step as per USP <71>
- Switch to bottles compatible with the ---(b)(4)--- system which contain neutralizers absorbing antibiotics. However, the only bottles commercially available at this time are ----------(b)(4)----------.

Reviewer Comments: *Without the above validation experiments and data the sterility tests performed for Ducord products originating from donors on intrapartum prophylaxis may be unreliable as the residual antibiotics may interfere with or otherwise hinder the test making the assay not compliant with 21 CFR § 610.12 (b)(1).*

Reviewer Comments: *The proposed test method and release specifications using ----------(b)(4)---------- to determine the sterility of the Ducord final product is acceptable. However, the HPC, Cord Blood processed from cord blood units isolated from donors undergoing intrapartum antibiotic prophylaxis have not been tested in the validation study. The residual antibiotics in these test samples may interfere with the sterility test making the test not compliant with 21 CFR § 610.12 (b)(1), which may increase the chances of transmitting bacterial and fungal infections. Thus, we recommend that the applicant validate the sterility assay using a more representative sampling of processed cord blood. Without this validation, we recommend that Ducord products processed from donors undergoing intrapartum antibiotic prophylaxis be excluded from the licensed inventory. In addition, a warning should be put in the Ducord label regarding the potential of allergic reactions in β-lactam antibiotic-sensitive Ducord recipients.*

IDENTITY TESTING

Baby Gender

The gender of the baby must be reported, but does not affect acceptability of the HPC, Cord Blood. The baby's gender is checked to ensure the completeness of the documentation at time of birth. This information is also sent to the transplant center because it may be used for engraftment and chimerism studies. The recipient may need to be informed if his/her sex chromosomes were changed (in blood samples) after engraftment. This information is captured in the Donor and Delivery Form and is indicated for all units.

Human Leukocyte Antigen (HLA) Typing (Initial)

Human leukocyte antigen (HLA) typing is performed on a sample of red blood cells from the cord blood unit (CBU) after processing. The results from this initial typing are reported. They are critical to ensuring the identity of the final product and to enhancing the likelihood of a successful transplant through computerized matching with the potential recipient. Thus, in addition to the initial HLA typing that is performed on the sample above, at the time of inquiry by a transplant center, confirmatory typing is performed on a segment removed from the frozen Ducord product. These two results must be consistent to assure the identity of the product prior to shipment to the transplant center.

Method Validation:

The initial HLA typing assay is performed on all products manufactured by CCBB by a CLIA approved contract laboratory (----------(b)(4)----------). This laboratory is also accredited by the American Society for Histocompatibility and Immunogenetics (ASHI). All method validations are performed by the ----------(b)(4)----------. A member of the QA team at the CCBB periodically audits the (b)(4) to be sure it is qualified to perform this testing. CLlA ----(b)(4)----.

Reviewer Comment: *method description and validation are satisfactory, given that CLIA certified laboratories perform assay.*

Human Leukocyte Antigen Typing (Confirmatory)

The confirmatory HLA typing assay is performed on all products manufactured by the Carolinas Cord Blood Bank (CCBB) by a CLIA approved contract laboratory (----------(b)(4)----------). This laboratory is also accredited by the American Society for Histocompatibility and Immunogenetics (ASHI). All method validations are performed by the ----------(b)(4)----------.

Reviewer Comment: *(b)(4) proficiency and training data was provided upon request. Because laboratory is CLIA certified and personnel have demonstrated proficiency at their job additional validation is not necessary. Note: CCBB did provide data for frequency of non-confirmatory results (see process validation). If results for initial and confirmatory testing are not identical a third test is performed by an NMDP specified laboratory.*

ABO/Rh Typing

Trained CCBB Processing Laboratory personnel perform ABO/Rh typing on a sample of each cord blood unit after processing. The test is performed according to SOP-CCBB-LAB-030. This procedure uses ----------(b)(4)---------- to demonstrate the presence or absence of antigens on cells from the cord blood sample. Agglutination of red blood cells with a particular reagent indicates the presence of the corresponding antigen. ----------
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--------(b)(4)----------
----------.
Results are recorded on CCBB-LAB-022 FRM1 and are provided to transplant centers.

Specifications allow for all blood groups and Rh types. Results must be reported for identity purposes.

Samples: -(b)(4)- sample obtained at the time of ----------(b)(4)----------.

Quality Control: The main reagents used for the ABO/Rh typing tests described above are from ----------(b)(4)---------- and have been submitted to the FDA through a BLA or the 510(k) process.

On each day of use, reagent quality control is performed (CCBB-LAB-029) by testing all ABO/Rh reagents with a references standard sample of known blood type and Rh status. If quality control testing provides inconclusive results, the expiration dates of all reagents are checked and replaced with an in-date reagent if necessary.

Reviewer comment: *CCBB Processing Laboratory is CAP (College of American Pathologists) accredited and participates in proficiency assays from the CAP to help ensure the continued quality of this assay. (b)(4) assay validation was provided and was satisfactory. Only specific personnel trained in this assay perform ABO/Rh/(b)(4) testing.*

POTENCY TESTING

Total Nucleated Cell Count (TNCC)

TNCC is calculated by adding the absolute white blood cells (WBC) and absolute nucleated red blood cells (NRBC) which are obtained using the ----------
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----------(b)(4)----------

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Acceptance criterion: The current manufacturing process requires that an incoming cord blood unit must have --(b)(4)-- total nucleated cells prior to processing. And, Ducord products must have $\geq 9 \times 10^8$ total nucleated cells after processing. Ducord units that do not meet these specifications are excluded from banking and disposed of according to CCBB-LAB-005 (i.e. waste, training, research).

Sample: A (b)(4) sample of the -----(b)(4)----- cord blood is obtained upon arrival at the CCBB Processing Laboratory, and another is obtained ----------
----------(b)(4)----------
----------.

Assay method: ----------

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

----------.

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

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

----------.

***Note**: ----------(b)(4)----------. In addition, the SCL has an excellent performance record on CAP proficiency tests.*

Method Validation: Extensive validation reports were provided in the original BLA. Most of the validation studies were performed by the manufacturer. In order to ensure that CCBB personnel are proficient in ---(b)(4)--- operation, information pertaining to personnel proficiency was requested in the November 2011 filing letter. The Applicant responded in Amendment 005 that each new tech must complete (b)(4) TNCC counts using ----------(b)(4)---------- samples before being considered trained. All staff members undergo annual competency assessment on all procedures. Training records were confirmed during inspection. In addition, CCBB participates

in the CAP (College of American Pathologists) accreditation program, which includes inspection and participation in proficiency standards for a variety of methods, including TNCC. Currently, the CCBB has participated in three proficiency tests using the ---(b)(4)--- (with three different technicians running these tests), and all three results were found acceptable by CAP.

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

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

***Review comment**: The -(b)(4)- Instrument is FDA cleared for analysis of cord blood. Because the -(b)(4)- has 510k clearance CCBB didn't perform independent validation but provided the validation reports from the device manufacturer. CCBB personnel are extensively trained and tested for proficiency in operation of the instrument. In addition, CCBB has procedures in place for routine maintenance and calibration of the instrument and reagents. Thus, CCBB has demonstrated sufficient control and proficiency with the method and demonstrated that it is sufficient for its intended purpose.*

Viability

Cell viability of Ducord is measured on a sample of cells ----------(b)(4)----------. Viability is measured using a ---(b)(4)--- assay (according to SOP CCBB-LAB-025 and STCL-SOP-022; Data is recorded on CCBB-LAB-025 FRM2 and CCBB-LAB-022 FRM1). ----------(b)(4)----------.

> ***Note:** SOP CCBB-LAB-025(used by CCBB Processing Laboratory) and STCL-SOP-022 (used by Duke Stem Cell Laboratory) are essentially the same procedure.*

Acceptance criterion: All Ducord product must have (b)(4) viability by --------(b)(4)---------- assay. Ducord units that do not meet specification are excluded from banking.

Sample preparation and method: ----------(b)(4)----------

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Method Validation: The Applicant initially did not think validation was necessary, stating that the CCBB participates in CAP proficiency exercises for this assay and that this testing provides ongoing quality control for the viability assay. CAP results are reviewed by the Laboratory Management to ensure accuracy and any discrepancies are recorded, investigated, and appropriate corrective action is taken.

Reviewer comment: *This was not considered an acceptable form of method validation and a validation protocol for this assay was requested in the November 2011 filing letter. During the t-con on 1-6-12 we encouraged the applicant to submit the validation protocols prior to initiation of studies. FDA commented on SOP and validation protocol during t-con on 1-24-12. The applicant submitted the validation data discussed below to the file in amendment 008, on June 1, 2012. The validation of this assay was considered especially important because this is a critical product quality attribute and very high viability numbers are consistently obtained from CCBB both pre-cryopreservation and post-thaw.*

Viability Validation Part II: Parameters assessed as part of the final validation protocol included accuracy, precision, specificity, limit of quantitation, linearity, and range.

Variables evaluated: ----------
----------(b)(4)----------
----------.

Sample preparation:

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

---------**(b)(4)**----------**:**

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

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

----------**(B)(4)**----------

(b)(4)

(b)(4)

Review Comment: *The --(b)(4)-- assay showed acceptable variability for the parameters measured. Thus, this validation demonstrates that the CCBB --(b)(4)-- assay is well-controlled*

and suitable for its intended use. Table 12 summarizes the coefficients of variation (CV) for each parameter assessed as well as the acceptance criteria that had been pre-defined in the protocol. Data collected for all parameters met specifications. As part of the validation exercise, the Applicant also discussed additional controls (i.e. QC on (b)(4), operator training). This validation is acceptable.

Viable CD34+ Quantitation

Executive summary
The ----(b)(4)---- assay is used to assess product potency, through measurement of viable CD34+ cells using the ---(b)(4)---. Most of the issues identified in the mid-cycle review were resolved in telecons with the Applicant from 5/15/2012 and 7/17/2011. The Applicant sent in further information on ---(b)(4)--- assay validation in submission 125407.008 on June 1, 2012 and 125407.010 on June 27, 2012. This information is reviewed below. The validation studies and supporting information are acceptable.

Note: *In the original submission, the Applicant provided data on accuracy, precision, linearity and range as well as limited data about inter-operator and inter-instrument variances of the CD34 enumeration assay for the (b)(4) and CD34, ------(b)(4)-------- assays. However, during the inspection in February 2012, the applicant indicated that they decided to use (b)(4) to enumerate CD34+ cells as the potency assay instead of ----------(b)(4)----------.*

The CD34+ antigen is present on immature hematopoietic precursor cells and on the majority of progenitor cells giving rise to hematopoietic colony forming units in umbilical cord blood. Under the FDA's Guidance for Industry Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications (October 2009), a minimum viable CD34+ cell content of $1.25x10^6$ cells per cord blood unit (CBU) is required. The CCBB utilizes a 510(k) cleared kit, the ----------(b)(4)---------- for enumeration of viable CD34+ cell content of each cord blood unit processed to determine cord blood potency and eligibility for banking and licensure. The (b)(4) kit is 510(k) cleared for cord blood units that were (b)(4) old; In the current validation study, the CCBB validated this assay in their laboratory, on the three ----------(b)(4)---------- run by three operators, they also validated the (b)(4) assay on cord blood samples up to (b)(4) old. The assay is performed in the Duke Stem Cell Laboratory (SCL), a CLIA-certified and CAP and FACT accredited laboratory of Duke Hospital which performs harvesting, processing, testing, cryopreservation, thawing, and release of HSCT products transplanted to patients treated within the Duke Health System.

Acceptance criteria: For potency assay (CD34+ cell enumeration): Each processed CBU must contain $\geq 1.25 \times 10^6$ viable CD34+ cells in order to be considered for release.

Sample preparation and method: ----------
-------(b)(4)----------
----------.

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

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

2 pages redacted (b)(4)

Overall Reviewer Assessment for ------(b)(4)-------

The Applicant has provided sufficient information about the -----(b)(4)------ assay used to measure CD34 cells, and they have adequately validated the -----(b)(4)------ assay portion of their potency assay. In addition, the SOPs, instrument qualification, reagent qualification, and quality controls of the assay are provided to ensure consistent performance of this assay as part of manufacturing. The -----(b)(4)------ laboratory has provided adequate information about procedures for instrument quality control, instrument validation, and training of staff. The Applicant has adequately demonstrated the accuracy, precision, linearity, and limits of detection for the --------(b)(4)--------- assay.

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

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

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

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----------**(b)(4)**----------
----------.

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

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

----------(B)(4)----------

Redact 1 page (b)(4)

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

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

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Reviewer Comment: *Satisfactory. Please see TNCC above for validation information.*

STABLILITY PROGRAM

The stability program submitted in the original BLA to determine the initial expiration date for Ducord (see details in the Expiration Date section of this review); and the stability protocol (i.e. testing plan to extend expiration date) were not acceptable. Following many discussions with the review team, the applicant revised their stability program. The applicant submitted protocol: *Carolina Cord Blood Bank Stability Protocol 2012-001-A* as part of Amendment 012 and the revised stability data analyzed using this protocol was submitted in amendment 013. The same data analysis plan described in the stability protocol was used to determine the initial expiry date and will be used going forward to extend the expiration date on a (b)(4) basis if warranted.

Reviewer Comment: *The applicant submitted a revision to the Stability Protocol on October 2, 2012, in amendment 021. The applicant revised the storage temperature to ≤ -150°C in the protocol. This does not affect the stability protocol or data analysis described below because all Ducord units are stored in the liquid phase of the liquid nitrogen freezer which is (b)(4).*

Overview of Carolina Cord Blood Bank Stability Protocol 2012-001-A

The CCBB stability protocol describes a prospective analysis of analytical data obtained from HPC, Cord Blood units before and after cryopreservation. However, the applicant has proposed an alternative to thawing a random sampling of HPC, Cord Blood units from the bank's inventory to perform stability testing. The applicant proposed that the analytical data for stability evaluation be collected from HPC, Cord Blood units when they are thawed for transplant at the

Duke Medical Center (i.e. Duke to Duke transplants). The applicant reasoned that this was acceptable for the following reasons. The same kind of data (see Table 16) that would be obtained from thawing and testing randomly selected HPC, Cord Blood units from the inventory is already collected on all units that are processed at CCBB and transplanted at Duke. And, that all HPC, Cord Blood units transplanted at Duke are prepared for infusion at the Duke Stem Cell Laboratory (SCL) using validated procedures. And, that the number of Duke to Duke transplants performed each year would provide sufficient data to evaluate the long term stability of Ducord without thawing additional HPC, Cord Blood units.

Note: *The applicant expressed great concern during nearly every interaction that a potential life saving HPC, Cord Blood unit would be thawed to perform QC testing for stability.*

Stability Protocol Execution

Carolina Cord Blood Bank Stability Protocol 2012-001-A defines the samples, tests, and specifications used to monitor the stability of HPC, Cord Blood products manufactured by CCBB as well as Ducord storage conditions. All Ducord products are stored in liquid nitrogen at the recommended storage temperature of ≤-150°C. Data included in the stability program is collected from units that are banked by the CCBB and transplanted at Duke University Medical Center (DUMC). Of the units distributed by the CCBB each year, about -(b)(4)- are transplanted at DUMC. For these units, both pre-cryopreservation, and post thaw analytical testing will be performed by the Duke Stem Cell Laboratory (SCL). Pre-cryopreservation analytical data is obtained from samples collected from the post-processing cryobag. Post-thaw analytical data is obtained from samples collected from the post-thaw/wash infusion bag. The validated tests performed by the SCL to obtain the analytical data are described in the Lot Release section of this review.

Note: *Until recently all HPC, Cord Blood units transplanted at Duke have been prepared for infusion at the SCL using the validated process outlined in STCL-SOP-028 (CCBB-DIST-028) and described in the Thaw and Wash section of this review. However, the SCL recently implemented a second procedure (STCL-PROC-036: Thawing and Washing Umbilical Cord blood Unit using an ----------(b)(4)----------). STCL-PROC-036 is used for HPC, Cord Blood units stored in (b)(4) bags (i.e. all CCBB processed cord blood) and STCL-SOP-028 ((b)(4) thawing procedure) is used for recipients weighing --(b)(4)-- and when the UCB unit that does not come in a (b)(4) bag (i.e. units from other banks).*

Reviewer Comment: *All the data presented in the Expiration Date section of this review was collected using the -(b)(4)- procedure outlined in STCL-SOP-028. However, going forward stability data will be collected from units thawed using the --(b)(4)-- procedure (STCL-SOP-036). Duke submitted data supporting validation of this procedure as well as comparability data for the ---------(b)(4)--------- procedures in amendment 019 on September 24, 2012. The ---(b)(4)--- procedure was found to be superior for % recovery of (b)(4) and TNCC and equivalent for CD34+ recovery. The ---(b)(4)--- procedure also demonstrated safe (no sterility failures) and efficient (reduced time and handling) processing which should not have an adverse affect on assessing stability in the future. Thus, data may be collected for the stability program using either the --------(b)(4)-------- thawing methods at the SCL.*

Sampling Plan: HPC, Cord Blood products included in the stability assessment will be randomly selected from units that were banked by the CCBB and transplanted at Duke University starting 10 years prior to initiation of the protocol. At least (b)(4) units will be evaluated for each storage year. If more than (b)(4) units are transplanted at Duke from a given storage time period, (b)(4) units will be randomly selected from the list of transplanted units following a pre-set randomization procedure. If less than (b)(4) units are selected for transplant at Duke from a given storage time period, additional units will be selected from the inventory at random, thawed, and analyzed according to the protocol.

Excluded units: Cord blood units with rare product characteristics will be excluded from random selection for thawing. The rare product characteristics pre-defined by the Medical Director include: rare HLA type, non-Caucasian donor and TNCC ---(b)(4)---. If a randomly chosen unit has any of the above characteristics, that unit will be excluded from selection and the next randomized number will be selected. Initially, unlicensed units (i.e. distributed under IND) will comprise the majority of the units tested since only a limited number of licensed units will be available. Each year, a greater proportion of licensed units will be represented in the test sample. For approximately 10 years at least some of the units tested under this protocol will be distributed under IND.

Reviewer Comment: *The sampling procedure is sufficiently meet protocol requirements.*

Randomization procedure:
Briefly, for storage years with more than (b)(4) Duke-to-Duke transplanted units, the transplanted units for the year will be sorted and randomized by UPN (Unique Patient Number).The UPN number is a number assigned by the Duke University Pediatric Blood and Marrow Transplant Unit for transplant patients and not considered a unique identifier of patient information in the CCBB.

For each year in storage with less than (b)(4) units transplanted (Duke to Duke), all transplanted units will be included in the analysis, and additional units will be randomly selected from the inventory, thawed and analyzed as described below to meet the (b)(4) unit requirement. For the additional units to be selected from the inventory, the units will be sorted and randomized by years in storage. If any of the units need to be excluded due to rare product characteristics then the next randomized unit will be selected.

Reviewer Comment: *The randomization procedure was sufficiently described in the protocol.*

Analytical Assays
The following analytical assays will be utilized to assess stability of Ducord. Specifications are based on the analysis of (b)(4) cord blood units banked by the CCBB from 1998 to the present and transplanted at Duke after 1-10 years in storage (data analysis provided in Expiration Date section of this review). Statistical analyses for minimum/maximum values, mean and SD are examined for the data based on time in storage.

TABLE 15: SPECIFICATIONS FOR STABILITY PROGRAM

Assay	Comparison	Method	Specification**
% Recovery TNCC	Comparing the percent recovery from testing at the SCL* (after thawing) to CCBB data (post-processing)	------(b)(4)-------	---------- --(b)(4)-
-----(b)(4)-----	----------(b)(4)---------- ----------(b)(4)---------- ----------	-----(b)(4)-----	--(b)(4)-
% Recovery Viable CD34+	Comparing recovery from SCL (after thawing) to SCL data post-processing	----------(b)(4)------ ---------	------ (b)(4)---
Post- thaw Viability	N/A. viability by STCL-SOP-022 on post thaw samples	----------(b)(4)------ ---------	(b)(4)
Sterility	Sterility of the thawed unit	------(b)(4)------	No Growth

* SCL: Duke Stem Cell Laboratory (SCL)
**If (b)(4) units meet specifications then an addition (b)(4) newly thawed units (b)(4) will be randomly selected and evaluated.

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

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Reviewer Comment: *The stability protocol outlined above is sufficient to determine the ongoing stability of Ducord stored at ≤-150°C in the BioArchive System. While, a pre-set acceptance rate for failures in a stability analysis is generally not acceptable, the applicant's own analysis of data did not reach this rate (see Expiration data section of this review). Moreover, units that fail to meet quality standards will not be transplanted. The applicant assesses potency from an attached segment prior to shipment of HPC, Cord Blood units and TNCC and viability are routinely assessed on thawed unit prior to transplant. The applicant is also performing assays for the stability analysis that are not required according to the guidance ((b)(4) recovery of viable cells). The data described in the Expiration Date section of this review supports a 7 year expiration date for Ducord, giving the applicant time to revise the stability program going forward if necessary.*

Note: *Analytical testing and storage conditions are consistent for HPC, Cord Blood units processed at CCBB. However, there were changes to manufacturing (i.e. ---(b)(4)--- process introduced in 2007, --(b)(4)--). Comparability studies provided with the original submission indicate that manufacturing changes did not significantly affect product quality.*

STABILITY DATA ANALYSIS FOR EXPIRATION DATE

As described above, the stability data submitted to support the expiration date for Ducord in the original application were found to be unacceptable. Briefly, the original submission contained a retrospective analysis of post thaw product recovery and engraftment data obtained for all HPC, Cord Blood that had been processed by CCBB and transplanted over the past 12 or more years. There were multiple issues with the original data in particular; over (b)(4) of the units in the dataset were shipped to non-Duke transplant centers. Thus, the majority of the post thaw data was supplied by outside transplant centers, and Duke could not demonstrate control of the methods used or validity of the data. Thus, the data was insufficient to provide a reliable determination of the ongoing stability of HPC, Cord Blood stored long term by CCBB, which was necessary to set an expiration date for Ducord. Additional stability data and a revised protocol to support long term stability was requested in the filing letter (see letter dated November 2011), and in a teleconference on 1-6-12.

Note: *During the 1-6-12 teleconference, Duke opposed sacrificing HPC, Cord Blood for QC testing, reasoning that these units should remain available for transplant. Duke argued that they had analyzed and submitted post-thaw data on thousands of HPC, Cord Blood units that had been produced by CCBB and used for transplant. And, that the data supported the long term stability of HPC, Cord Blood processed by CCBB and proposed a (b)(4) expiration date. Duke was informed that because they could not validate close to (b)(4) the data, the data was not acceptable as submitted. Duke proposed using a subset of the submitted data, which was obtained for HPC, Cord Blood units that were processed by CCBB and transplanted at Duke (i.e. Duke to Duke transplants). For these units, the Duke Stem Cell Laboratory (SCL) performed both pre-cryopreservation and post-thaw HPC, Cord Blood product quality analyses using validated assays. They stated this would allow for greater control of the methods and thus, more valid data. Duke was requested to submit a protocol describing how they would perform a prospective analysis of the historical data; and informed that the protocol must include at a minimum pre-set acceptance criteria for product quality attributes, a defined sampling regime and a data analysis plan. Such an analysis plan had the potential to provide a sufficiently robust analysis of the long term stability of the banked HPC, Cord Blood, thus, allowing Duke to determine an expiration date based on their historical data. We supported this approach given the significant amount of data, albeit, not entirely comprehensible, that Duke had acquired to support long term stability; and given that the pre- and post- thaw analyses were performed by the SCL using validated assays. However, the applicant was informed that data review was necessary before acceptability could be determined. A draft protocol for a prospective analysis of historical stability data was discussed during the facility inspection on 3-2-12.*

Note: *The draft protocol included a prospective analysis of product recovery data obtained from HPC, Cord Blood units that were banked by CCBB and transplanted at the Duke Medical Center (Duke to Duke transplants). The analysis plan provided a direct comparison of pre-cryo and post-thaw product quality attributes, including TNCC recovery, % viability, % CD34+ viability, and (b)(4), with pre-determined acceptance criteria. The sampling plan included using 3 randomly selected HPC, Cord Blood units from each year of processing going back from the start of the protocol (March 2012).*

Results: Duke submitted the stability data analysis protocol and data analysis summary including post thaw recoveries and post-transplant engraftment data in Amendment 008, on June 1, 2012. Briefly, post-thaw recovery data (i.e. recovery of TNC, % viable CD45+ cells, % ----------(b)(4)----------) was obtained from samples taken from the attached segments not from units prepared for transplant in the SCL. The data analyzed was obtained from assays performed in the Potency Lab (not the SCL), using assays that were not validated. The applicant also included engraftment data, which was obtained from transplant centers around the country and depended on factors beyond Duke's control. And, the applicant stated that if a unit passed ----(b)(4)--- acceptance criteria for the assays used to measure stability, then the unit would pass. Based on this data Duke concluded that post-thaw recoveries do not decline over time and that current clinical data supported a minimum of a 7-year expiry period. Duke stated that data from (b)(4) years in storage was also analyzed, but the numbers were too small to give statistical confidence.

Reviewer comment: *The stability data analysis submitted by the Applicant in Amendment 008 was not acceptable. The analysis performed was not consistent with the draft protocol discussed in March 2012 and included data from assays that have not been validated (i.e. segment and engraftment data).*

Note: *During additional discussion held on July 17, 2012 and July 20, 2012 the applicant revised the stability data analysis protocol described in amendment 008 to a protocol more reflective of the draft proposal agreed to in March. Duke requested that acceptance criteria be set for the overall stability program based on historical data (i.e. (b)(4) of the units tested must pass all criteria). Stability data used to support the expiration date for Ducord was provided in Amendment 013 on August 10, 2012.*

Revised Stability data analysis for expiration date determination

The stability data analysis provided in amendment 013 was performed according to the Stability protocol outlined above (*Carolina Cord Blood Bank Stability Protocol* 2012-001-A (27 Jul 2012). For the stability data analysis TNCC recovery, viability, CD34+ recovery, sterility, and (b)(4) data were collected from units that were processed by CCBB and transplanted at Duke (Duke to Duke transplants). This allowed for control of the data collected since similar if not the same analyses were performed pre-cryopreservation and post-thaw. The analysis for expiry date included units that had been transplanted over the past (b)(4) years. Data was organized based on time in storage. Duke proposed a 7 year expiration date.

Reviewer comment: *While the use of a prospective analysis of historical data is not frequently used to determine expiration date, the Applicant provided sufficient rationale to support this data analysis plan. Briefly, data were available for hundreds of units processed at CCBB and transplanted at Duke. The applicant had demonstrated sufficient control of the assays that would be used to determine stability (see review of assay validations in the Lot Release sections of this review). The planned analyses eliminated the need to thaw additional units to collect post-thaw data, units that the applicant argued may be necessary for future transplants.*

Description of the Stability Data Analysis:

Analytical tests: The data analyzed to assess stability and set expiration date were outlined in Table 16 and include: % recovery of total nucleated cells post thaw; % recovery of CD34 cells post thaw; ---------(b)(4)----------; % viability and sterility post thaw. Methods are described in the Lot release section of this review.

Sample Selection: For units to be included in the prospective data analysis they had to meet the criteria listed below:

- Transplanted as a single cord blood unit
- Be administered after myeloablative chemotherapy
- Be not more than minimally manipulated post thaw and wash
- Be a first cord blood transplant for the patient
- HPC, Cord Blood units banked by the CCBB and transplanted at Duke.

HPC, Cord Blood Databases: Two data sets were collected and evaluated to determine the initial expiration date. The first data set included data from all Duke to Duke transplants over the past (b)(4) years (Total Dataset). This database included (b)(4) HPC, Cord Blood products that met the sample selection criteria listed above. The second dataset included a pre-determined number of randomly selecting units (b)(4) that must meet pre-set sample selection criteria (Random dataset). This database included (b)(4) HPC, Cord Blood products transplanted over the past (b)(4) yrs. For the Random dataset, cord blood units were selected using the randomization strategy defined in 2012-001-A and described above.

ANALYSIS OF THE TOTAL DATASET ((B)(4) SAMPLES)

Table 16 below summarizes the analytical data obtained for the total dataset consisting of (b)(4) HPC, Cord Blood units. Average values per year in storage are shown with Standard deviations (SD) and % of units that met acceptance criteria. The yearly minimum and maximum values, % meeting acceptance criteria and number of units that failed each test are provided in the assay summaries below Table 16. There was no indication that failures were related to time in storage, as there was no trend indicated for any particular year.

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(B)(4)

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(b)(4)

----------**(b)(4)**----------.

Expiration date proposed

Duke proposes a 7 year expiration date based on data submitted in the original submission and total -(b)(4)- and random datasets, with the possibility of extending ----------(b)(4)----------.

In addition to the data provided above, Duke presented supportive data in the original submission from transplanted HPC, Cord Blood to support stability.

Reviewer Comment: *The data presented supports the 7 yr expiry date. The data does not indicate a loss of activity during the (b)(4) period studied based on the analyses performed. However, because (b)(4) or more units were not available for analysis for years (b)(4), Duke proposed 7 yrs as expiration date. Going forward Duke proposes to evaluate (b)(4) units per given year of storage from 2005 forward for the possibility of extending the expiry ----------(b)(4)----------. One caveat to the data analysis plan is the acceptance criteria of (b)(4) units must pass all specifications to pass stability. However, in addition to the stability analyses, Duke has other assurances that Ducord units with low potency will not be transplanted. Ducord will be tested for % TNCC and viability at most transplant centers prior to transplant. And, Duke performs in house potency tests for ----------(b)(4)---------- prior to sending HPC, Cord Blood units to transplant centers.*

STABILITY OF THAWED HPC, CORD BLOOD PRIOR TO TRANSPLANT

The data provided by CCBB to support post-thaw/wash stability were obtained from published manuscripts and not from an empirical study performed with Ducord. However, the thaw/dilute/wash methods described in the manuscripts were the similar to those used at CCBB and CCBB/Duke personnel participated in the research described. The published data supports a ~6 hr time limit on thawed/diluted and washed HPC, Cord Blood units stored at 18-25ºC. However, Duke has conservatively set the expiration time and storage temperature for a diluted and washed unit stored at 4-8°C as ≤ 4 hrs.

----------**(b)(4)**----------.

Reviewer comment: *The proposed time limits for thawed, diluted, and thawed and washed Ducord units are acceptable and within the range demonstrated by the data provided.*

RETENTION SAMPLES

Duke describes various samples that are retained for each HPC, Cord Blood that is shipped for transplant. ----------(b)(4)----------.

Reviewer Comment: *Duke has adequate retention samples which are properly stored.*

CONTAINER CLOSURE SYSTEM

All containers and closures that are in direct contact with the HPC, Cord Blood products are sterile and FDA approved devices (see table below). All product contact materials (for both the CCBB Collection sites and the CCBB Processing Laboratory) are received, inspected, and stored by trained CCBB personnel according to SOP COMM-QA-001.

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

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Reviewer comment: *Containers and closures were adequately described and all licensed containers are used for product contact. Proper storage and quarantine were observed during the PMI (see OCBQ review for details).*

FINAL CORD BLOOD UNIT RELEASE / DISPOSITION

Prior to release of the CBU to long-term storage, the manufacturing file for the unit is reviewed on multiple levels according to SOP CCBB-QA-045. The first review for quality of the package is performed by Clinical Research Coordinators. The CCBB Operations Manager or designee performs a second quality review. CCBB Medical Director performs a technical review and determines donor eligibility, and a final review is performed by a designee of the Quality Systems Unit. The QSU review ensures that all reviews are completed and all required specifications are met. The Exclusion and Quarantine Release Form (CCBB-QA-045 FRM1) is used to aid in the review of the manufacturing file.

The initial quality review of the product file (batch record) includes confirming that all barcodes match, copies of applicable pages of the batch production record are confirmed to be printed from -(b)(4)-, original source data pages from the batch production record match the printout from -(b)(4)- and are included in the file, test results are uploaded and printed and pass specifications, donor consent is reviewed. At any time if specifications are not met, the unit can be excluded from long-term storage and disposed of according to LAB-CCBB-LAB-005. The Medical Director performs the same review along with a more in-depth review of all test results, newborn information and medical history review. Once the Medical Director signs the release of the unit into long-term storage, the information from the --(b)(4)-- database is provided to NMDP.

Note: *The -(b)(4)-- computer system manages Duke's cord blood unit manufacturing database. For registry listing purposes alone, -(b)(4)-- passes listing data from the Duke database, to the NMDP, for inclusion on the NMDP Registry. The -(b)(4)-- system has a backup search system for all units banked in the CCBB. This was originally created as part of the COBLT study and was used for donor searches conducted for patients on the COBLT transplant study from1999-2004. After that time, the NMDP--(b)(4)-- interfaces were created and the CCBB units were listed on the NMDP. All subsequent searches have been conducted through the NMDP Traxis system. The Duke Transplant programs utilize the -(b)(4)-- search system as a backup system to verify that CCBB units listed through NMDP appear on the NMDP search. However, since 2004, all units are selected from the NMDP search system, not the local system. All other transplant centers search and select units through the NMDP.*

Registry listing and Quality Unit release

Each lot of Ducord is maintained in the ThermoGenesis BioArchive under virtual quarantine until all results for donor eligibility, collection, processing, cryopreservation and testing are reviewed as acceptable for banking. Prior to uploading to the National Marrow Donor Program (NMDP) search registry the records for each lot of Ducord are reviewed according to CCBB-QA-045 Quarantine to Long Term Storage Exclusion Release Procedure and documented on CCBB-QA-045 FRM1. This procedure ensures that each Ducord unit meets all donor eligibility screening and testing according to 21 CFR Part 1271 regulations (as outlined above) and quality control acceptance criteria (see Table 3).

Selection, release and transport to the transplant facilities are described in SOP CCBB-DIST-025, DIST-026, DIST-027and include related SOPs CCBB-DIST-028, CCBB-DIST-002 and DIST-002 FRM2. These procedures are outlined below.

Inventory Search

Ducord products that meet donor elibibility (DE) and release criteria are qualified for long-term storage and are HLA typed. As described in SOP CCBB-DIST-025, information about qualified Ducord units is placed in the National Marrow Donor Program (NMDP) searchable web-based data base which is searched using the Traxis™ system, and is managed by ---(b)(4)---. Ducord product data can be accessed by registered transplant center (TC) coordinators, treating physicians, and TC medical directors only.

Product Selection

A transplant center representative or treating physician informs CCBB of their interest in a prospective Ducord product based on HLA type listed in the database. The system has a built-in feature that prevents a donor from receiving their own cord blood. Briefly, if the donor and patient are a perfect HLA match, ----(b)(4)--- validates the match, and a pop-up box appears to the Search Coordinator at NMDP (SC) alerting them. The SC provides CCBB with patient information (e.g. name, parent's name, and date of birth) to determine if donor and patient are the same. If the Ducord unit is not to be from the patient, the search resumes and Ducord can be ordered by the transplant center. If the Ducord product is from the patient, the Ducord product is medically deferred and excluded from the registry per SOP CCBB-LAB-005.

After a potential Ducord unit is identified, CCBB is contacted by NMDP and asked to provide a sample for confirmatory HLA typing and, possibly other quality data (e.g. cell counts, viability, CD34, (b)(4)). CCBB uses an attached segment, which is removed according to SOP CCBB-DIST-020, *Removing Segments from Cord Blood Units* for HLA confirmatory testing and potency testing (i.e. CD34+ --------(b)(4)-------- enumeration). Post-cryopreservation potency testing is currently performed by CCBB for information only. When the requested information is obtained and the HLA typing is confirmed, the transplant center can release the unit, put it on hold or order the unit for their patient, and request shipment of the Ducord product to the transplant center.

Ordering and Release

When a Ducord unit is requested by a transplant center, NMDP coordinates with CCBB to arrange for shipping as described in SOP CCBB DIST-026. NMDP provides required forms (i.e. NMDP Cord Order Form (Form F00067), CBU Review and Preliminary Risk Assessment Form, Cord Blood Unit Confirmatory Typing Report (HLA report), NMDP Form 117 Final Recipient HLA Typing, other forms and documents unique to a particular transplant center (these vary by TC) or country) to CCBB personnel who then initiate the order. CCBB completes the Order Request checklist (CCBB-DIST-026 FRM1), retrieves of the Ducord file (batch record), ensures that the Cord Blood Unit Specification CCBB-DIST-002 FRM2 has been completed and signed, confirms a shipping date between the CCBB laboratory and NMDP/TC coordinator, prints and completes the necessary NMDP paperwork (i.e. NMDP product insert,. Final declaration of donor eligibility and Maternal IDM report, risk assessment form [PRA]), generates ISBT barcodes, labels the paperwork, verifies labels, assembles the complete Ducord shipping package, ensures a dry shipper is charged and arranges shipment with courier.

Transport to the Transport Center

CCBB coordinates with the transplant center (TC) regarding initiation of shipping the Ducord product (SOP DIST-027) and receipt at the TC (CCBB DIST-022). A packet of accompanying

paperwork (see above) is prepared to accompany Ducord to the TC. A validated dry shipper (see shipping validation) is charged 24 hours or more prior to the planned date of shipment.

On the day of shipment, Ducord is removed from the ThermoGenesis BioArchive®, visually inspected by two technicians to confirm identity, proper labeling and integrity of the cassette, bag and segments and photographed (see Figure 5). After inspection, Ducord is placed in the dry shipper. The lid with temperature logger is placed inside. The package insert is placed inside the lid of the dry shipper. The paperwork for the courier (FedEx or other carrier) is completed. The shipper is sealed with zip ties and photographed. The courier picks up the dry shipper and transports to TC.

Receipt and storage

Upon receipt, the Transplant Center (TC) is instructed (CCBB-DIST-022) to inspect the Ducord metal cassette, verify labeling information, and transfer the Ducord product to the vapor or liquid phase of liquid nitrogen as fast as possible. The TC notifies the CCBB that the HPC, Cord Blood was received and provides feedback on its condition by filling out and faxing the NMDP Form 600 to the CCBB laboratory. The TC returns dry shipper to CCBB.

Infusion

On the day of transplant, the Ducord is thawed, sometimes washed (at the discretion of transplant center) and infused. The applicant provides detailed instructions for thawing and emergency product recovery with the package insert, which is sent to transplant center with Ducord (reviewed above). Reactions to infusion within the subsequent 24 hours are scored and reported to CCBB immediately. Recoveries of nucleated cells, viable cells, CD34 cells and (b)(4) are enumerated at the TC and reported back to CCBB. Sterility cultures of the infused product are also obtained by the transplant center and reported to CCBB. Procedures at individual transplant centers are not a part of this license application and are not reviewed.

Reviewer comment: *The SOPs and narratives related to registry listing, selection, and shipping are acceptable. There are multiple checks and rechecks to ensure that the proper Ducord unit and paperwork will be provided to the transplant center.*

ENVIRONMENTAL ASSESSMENT

The Applicant requested a claim for categorical exclusion for Ducord product in this Biologics License
Application as provided for in 21 CFR Part 25.31(c) in that action on this application is for substances that occur naturally in the environment. The action does not alter significantly the concentration or distribution of the substances, its metabolites, or degradation products in the environment. Please DMPQ review of the applicant's claim for categorical exclusion.

COMPUTER SYSTEMS

The main computer system in use at CCBB is the --(b)(4)- system that stores critical information on the manufacture and testing of HPC, Cord Blood. The --(b)(4)- system records results of

donor eligibility screening and testing, in addition to serving as the structure for all processing, cryopreservation, and storage information/test results for each HPC, Cord Blood.

--(b)(4)- serves as a web-based bank data management and inventory system. It was initially developed under a contract from the National Heart Lung and Blood Institute (NHLBI) under the Cord Blood Transplantation Study (COBLT) and has been upgraded and supported by the ---------(b)(4)------- through a contract with the CCBB since the completion of the NHLBI contract. See DMPQ review for additional details.

LABELING AND TRACKING

Donor tracking and labeling

Please see DE and collection sections of this review.

Prescribing Package Insert (PI)

The relevant CMC sections of the PI have been reviewed for accuracy. And, the Instructions for Preparation for Infusion are acceptable and follow the validated process based on STCL-SOP-028. A final approved word document of the PI was submitted to the file in amendment 020 on September 25, 2012.

Reviewer Comment: *The Instructions for Preparation for Infusion were found to be acceptable on October 1, 2012, amended to the approved PI and submitted to the application in Amendment 21 on October2, 2012.*

Package Labels

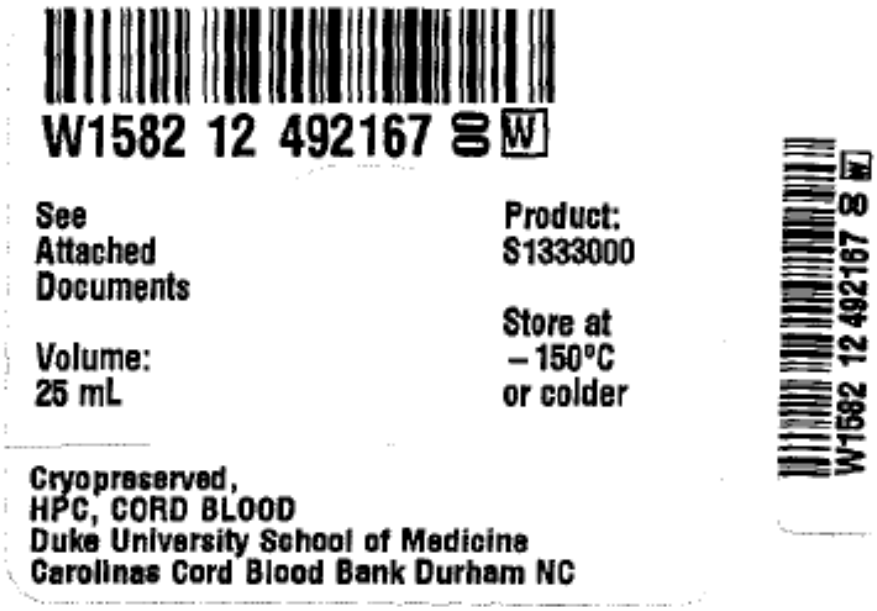
Ducord is labeled using an electronic barcode label called the ISBT 128 standard (ISBT label described under Collection Process section of this review) which is based on internationally agreed upon standards for data identifiers, data format information, and data pertaining to the product. All Cord blood units (CBU) collected by the CCBB are assigned a unique ISBT product identifier (according to SOP CCBB-DIST-036) prior to cord blood collection, and this number is utilized throughout the manufacturing process to label all related reagents, products and paperwork.

Partial Label

The final Ducord cryobag is labeled with the ISBT-128 label (according to CCBB-DIST-036) prior to sterile docking of the collection bag to the --(b)(4)-- processing kit, which includes the Ducord cryobag. Due to size limitations the cryobag is labeled with a partial label (21 610.60(c)) and must contain at a minimum the proper name of the product (i.e. HPC, Cord Blood), the name of the licensed manufacturer (i.e. Duke University School of Medicine, through CCBB) and the lot number (unique donor identification barcode) or other unique identifier. Duke plans to use the product code for Buffy coat enriched cryopreserved HPC, Cord Blood (S1333) for all Ducord products. The Ducord cryobag is divided into an 80% portion and a 20% portion, a larger partial label is placed on the 80% portion. The 20% portion of the cryobag contains only the smaller barcode label with the ISBT unique donor identifier (see example in Figure3 below). The

product code is listed in Figure 3 as S1333000, the product code is actually S1333 and 000 are place holders.

Figure 3: Barcode Label for Ducord cryobag (partial label)

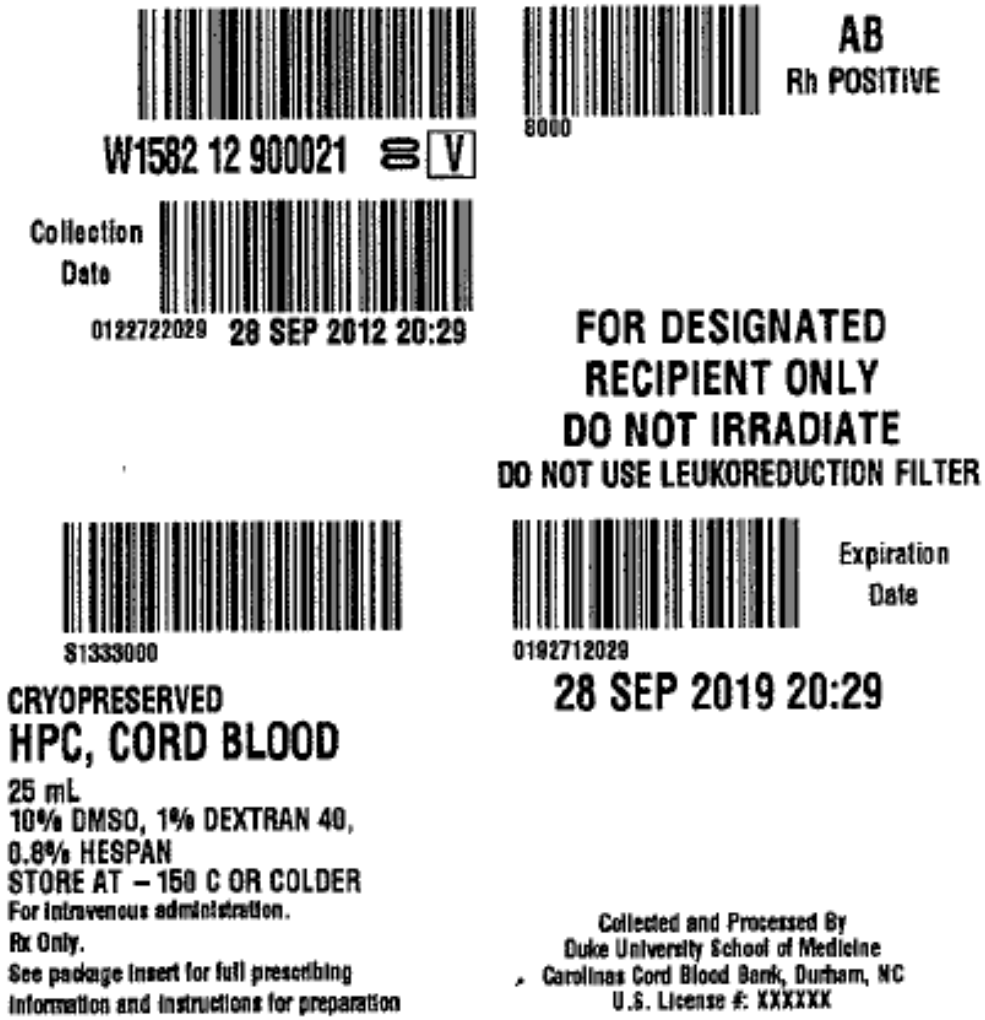


Reviewer Comment: *The partial label meets CFR requirements and is acceptable.*

Full Package Label

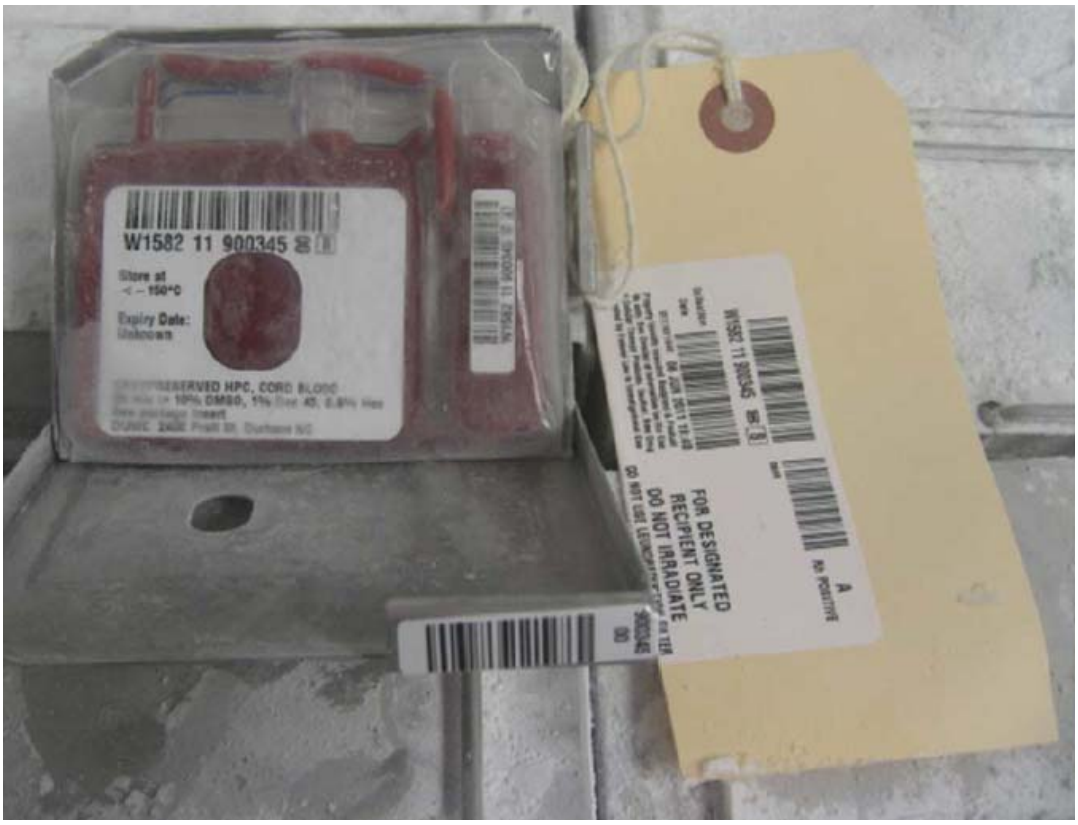
Ducord must also be labeled with a full package label as outlined in 21 CFR-610.61. Because the Ducord container is too small for the full package label, the full package label is attached to a tie tag that is affixed to the metal canister containing Ducord prior to shipping to a transplant center. The full label must contain the following information: proper name of product (HPC, Cord Blood), name and address of license number of the manufacturer, lot number or other lot identification, expiration date, the preservative if used and concentration, the amount of product (volume), storage temperature, other instructions (i.e. do not irradiate, etc), route of administration or reference to prescribing insert (PI), known sensitizing substances or reference to PI, inactive ingredients when a safety factor or reference to PI, source of product if relevant for safe administration, and statement: "Rx only". The tie tag contains the formal ISBT 4 quadrant barcode as shown below. The label is folded over the tie tag so that the two upper quadrants are on one side (donor and recipient information) and the two lower quadrants are on the other side (product and manufacturer information). The expiration date of 7 years and will be assigned to the label at time the product is shipped based on the collection date of the product.

Figure 4: Ducord Package Label (on Tie tag)



Reviewer comment: *Following discussion with the review team the final package label was revised to contain all required elements. The final package container label was submitted with Amendment 020 on September 25, 2012. The package label is acceptable. Package label has a placeholder for license number as applicant does not have that information at this time. License number will be added to the label when Ducord is approved. The license number is 1870.*

Figure 5: Example of Ducord Final Product



Reviewer comment: *Figure 5 represents an example of how Ducord will be shipped to transplant centers. The exact information on the attached labels does not match the final approved labels. This is acceptable since this is an example of the configuration.*