

MEMORANDUM

BLA 125657

CMC Review of Original Submission

Hematopoietic Progenitor Cells, Cord Blood (HPC, Cord Blood)

MD Anderson Cord Blood Bank

**Division of Cellular and Gene Therapies
Office of Tissues and Advanced Therapies**

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EXECUTIVE SUMMARY

Recommendation:

We recommend that the BLA be approved and the approval be granted only for HPC, Cord Blood units that will be manufactured after the approval date.

Based on our review and inspection findings, CGMP compliance was not demonstrated until the most recent revisions to the license application. Therefore, only units that will be manufactured after these revisions are implemented will qualify for licensure.

Product Overview:

Hematopoietic progenitor cells, cord blood (HPC, Cord Blood), is manufactured by the MD Anderson Cord Blood Bank at the University of Texas, Houston. Manufacturing and product quality standards for HPC, Cord Blood manufactured at MD Anderson are consistent with recommendations made in the FDA's HPC, Cord Blood licensure guidance.

The (b) (4) device is used to perform cord blood volume reduction and partial red cell and plasma depletion. The final product is a 25 ml total volume containing 10% DMSO and 1% Dextran 40. Each unit is frozen using a controlled rate freezing process and then stored in liquid nitrogen (b) (4). Final product is tested for purity, identity, sterility and potency.

The HPC, Cord Blood under this license will have a 10-year dating period. A (b) (4)

HPC, Cord Blood units are shipped frozen in special shipping containers (Dry-Shippers) designed to maintain a controlled environment and very low temperature ($\leq -150^{\circ}\text{C}$). Shipping must be completed within six days. Environmental temperature within the shipping container is electronically monitored and recorded for the entire transit time.

Although two alternative thawing and wash procedures have been validated, only the directions for the (b) (4) wash procedure will be included with each shipped unit of HPC, Cord Blood. The (b) (4) device wash procedure will be, however, used in-house for (b) (4) stability studies.

Review Findings:

A team of five reviewers evaluated the CMC information. This review is a compilation of all the CMC reviews. During the CMC review, several deficiencies were identified. These deficiencies were communicated to the applicant via letter comments and teleconferences. Examples of deficiencies include incomplete or inappropriate donor screening and testing, insufficient method validation, inadequate validation for the flow cytometry based assays, and inappropriate sample retention plans. All of the identified deficiencies have been adequately resolved. Based on the CMC review, the updated manufacturing controls meet all of the quality standards established in the cord blood licensure guidance and comply with CGMP.

BACKGROUND/HISTORY

MD Anderson initially submitted this BLA (under BLA 125642) on October 17, 2016. The BLA was not filed due to an overall lack of adequate content and poorly organized information that precluded a substantive and meaningful review of the BLA. In the 'Refuse to File' letter sent to the applicant on December 16, 2016, guidance was provided regarding information to be included in a future BLA submission. The applicant had a teleconference with the Agency on January 25, 2017 to seek further guidance and clarification. During the meeting, the applicant was advised that there is no need to distinguish between drug product and drug substance for HPC, Cord Blood submitted in the eCTD format. The firm was further advised to create appropriate subsections within eCTD modules and a table of contents for the modular document. The applicant indicated they would not seek a proprietary name. The applicant was informed that a new BLA number would be assigned because more than 30 days had passed since the 'refuse to File' notification. This current application is a 'resubmission'.

GENERAL INFORMATION

The MD Anderson Cord Blood Bank is owned by The University of Texas MD Anderson Cancer Center. The Cord Bank was established in April 2005 within the Cell Therapy Laboratory of the Department of

Stem Cell Transplantation and Cellular Therapy. Since then the bank has collected more than 83,000 cord blood donations, banked over 28,000 units and released more than 1,700 units for transplantation. The cord bank is registered with the FDA as an establishment of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) for Peripheral Blood, Donor Lymphocyte and Cord Blood as of 2017; the FDA Field Establishment Identifier (FEI) is 3010547404

The cord bank retains executed cord blood collection agreements with five hospitals in the metropolitan Houston area (local sites) and one hospital with two sites (remote sites) in Detroit, Michigan area (seven contracted collection sites total), namely: The Women's Hospital of Texas; Ben Taub General Hospital of Baylor College of Medicine; Memorial Herman Southwest; St Joseph's Medical Center; Memorial Herman Medical Center in Houston, and St John's Health System in Detroit. Local collection sites have a secured, dedicated collection room located in or near the labor and delivery unit at each hospital. At remote collection sites, cord blood is collected in a designated area in the delivery room. Trained collectors, including obstetricians and midwives, perform cord blood collection from consented mothers using in-utero and/or ex-utero collection procedures. Ex-utero collections are performed by dedicated cord blood bank staff.

Since establishment of the MD Anderson Cord Blood bank in 2005, (b) (4) manufacturing method has been used, i.e. volume reduction using the (b) (4) system. This is the method the applicant proposes for licensure in the BLA application.

The MD Anderson Cord Blood Bank Laboratory is accredited by the College of American Pathologists (CAP Number 8727764), and CLIA registered (CLIA Number 45D2062344).

MD Anderson uses outside labs for some safety and identity testing as indicated in the Table 1 below.

Table 1: List of Contract Testing Laboratories

Testing Facility	Testing Performed	Registration/Certifications
(b) (4)	(b) (4)	FEI: (b) (4) CLIA ID Number (b) (4) AABB Accreditation
The University of Texas MD Anderson Cancer Center Laboratory Medicine HLA Lab 6565 MD Anderson Blvd. Room (b) (4) Houston, TX 77030 713-792-2658	Human Leukocyte Antigen typing	ASHI Number: 04-5-TX-25-1 CLIA ID Number: 45D0492022 CAP Number: 2108111
(b) (4)	(b) (4)	CLIA ID Number: (b) (4) ASHI Number: (b) (4)

(b) (4)	(b) (4)	FEI: (b) (4)
(b) (4)	(b) (4)	CLIA ID Number: (b) (4) CAP Number: (b) (4)
(b) (4)	(b) (4)	CLIA ID Number: (b) (4) CAP Number: (b) (4)
(b) (4)	(b) (4)	CLIA ID Number: (b) (4) CAP Number: (b) (4)

Cross-Referenced Drug Master File (b) (4) for the (b) (4)

FACILITY DESCRIPTION

The Cord Blood Bank was established in April 2005 within the Cell Therapy Laboratory of the Department of Stem Cell Transplantation and Cellular Therapy. The current MD Anderson Cord Blood Bank facility located at 1841 Old Spanish Trail in Houston Texas was initially commissioned in July of 2013 and recommissioned in December 2015, subsequent to renovations.

The manufacturing facility and staff offices are located in approximately (b) (4) square feet of space in the Medical Support Facility (MSF) building. Over (b) (4) square feet of the ISO classified clean room facility is designated for the manufacture and testing of HPC, Cord Blood. All manufacturing activity for the production of HPC, Cord Blood is performed in an (b) (4) classified clean room. All manipulation is performed using a functionally closed system wherein the addition of excipients and removal of samples are performed using sterile connection devices.

A basic floor plan of the facility is included in the submission.

HPC, CORD BLOOD DESCRIPTION AND COMPOSITION

The final hematopoietic progenitor cells, cord blood (HPC, Cord Blood) product consists of a 25 ml frozen product cryopreserved in 10% DMSO, and 1% Dextran 40 and stored in liquid nitrogen ($\leq -150^{\circ}\text{C}$). Each HPC, Cord Blood unit is packaged in a two-compartment cryobag. The larger compartment contains 80% (20 ml) of the injectable suspension and the smaller compartment contains 20% (5 ml). The rationale for freezing the HPC, Cord Blood product in a two-compartment bag is to allow the removal of the smaller fraction for further manipulation without thawing the larger. Each HPC, Cord Blood unit contains a minimum of 9×10^8 total nucleated cells (TNC) and 1.25×10^6 viable CD34+ cells.

The HPC, Cord Blood is maintained in a protective steel canister, which is labeled and enclosed in a protective foam thermal sleeve. The units are shipped frozen in special shipping containers (Dry Shipper) which maintain interior compartment temperature at $\leq -150^{\circ}\text{C}$. The temperature is electronically monitored and recorded during the entire transit time.

The applicant has requested exemption from the NDC code; this is because of the use of the ISBT 128 compliant labeling. The UNII codes and names of the product are listed below.

Proprietary Name: None

Non-proprietary Name: hematopoietic progenitor cells, cord blood (HPC, Cord Blood)

Active Ingredient:

Cord Blood Hematopoietic Progenitor Cells

UNII Code:

XU53VK93MC

Inactive Ingredients:

Dextran 40

Dimethylsulfoxide (DMSO)

(b) (4)

UNII Code:

K3R6ZDH4DU

YOW8V9698H

(b) (4)

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

Dosage Form: Injectable Suspension

Table 2: HPC, Cord Blood Specification

Product Characteristics	Testing	Sample Type and Timing	Specification
	Infectious Diseases Testing Required (21 CFR 1271.45 through 1271.90)	Maternal blood sample obtained with 7 days of	All tests negative, except CMV

Safety	HBsAg Anti-Hep B core Anti-HCV Anti-HIV-1/2 Anti-HTLV-1/2 Anti-Trypanosoma cruzi (Chagas) HIV RNA/HCV RNA/HBV DNA West Nile Virus RNA Syphilis Cytomegalovirus (CMV)	cord blood collection. 21 CFR 1271.80 (a) (b)	CMV results-Report
	Sterility	RBC samples after processing (validated)	No growth at (b) (4)
	Hemoglobinopathy	(b) (4)	(b) (4)
Purity and Potency	Total CD34+ cell count	HPC, Cord Blood (pre-cryopreservation)	$\geq 1.25 \times 10^6$ /HPC, Cord Blood
	Total Nucleated Cell (TNC) count (per HPC, Cord Blood)	HPC, Cord Blood (pre-cryopreservation)	Pre-Process: (b) (4) Post-process: (b) (4)
	Nucleated RBC	HPC, Cord Blood (pre-cryopreservation)	(b) (4)
	Viability Nucleated cell (b) (4)	HPC, Cord Blood (pre-cryopreservation)	(b) (4)
	Viability- CD34+ cells (b) (4)	HPC, Cord Blood (pre-cryopreservation)	(b) (4)
	Colony Forming Units (CFU) assay	HPC, Cord Blood (pre-cryopreservation)	Growth
Identity	Initial Human Leukocyte Antigen (HLA)	HPC, Cord Blood (pre-cryopreservation)	Report
	Confirmatory HLA	Attached segment	Report
	ABO/Rh Type	Cord blood	Report
Volume	Cord Blood Volume at collection	Cord Blood	(b) (4)

CORD BLOOD COLLECTION

MDACBB currently collects cord blood units (CBUs) at 7 hospitals (5 in Houston, Texas and 2 in Detroit, Michigan). The hospitals in Texas are “local collection sites”; the hospitals in Michigan are “remote collection sites”. Cord blood is collected by trained collectors, including obstetricians (OBs) or certified nurse midwives (CNMs). Cord blood collections are performed after vaginal or C-section deliveries, using in-utero and/or ex-utero collection procedures.

Collection sites

The following is the current list of collection sites [BLA section 3.2.P.3.1-1]

Table 3:Cord Blood Collection Sites

Site Code	Site Address	Local/Remote	Distance from CBB
BTGH	Ben Taub General Hospital 1530 Taub Loop Houston, TX 77030 713-873-5374	Local	2-miles
TWHT	The Woman’s Hospital of Texas 7600 Fannin Houston, TX 77054 713-791-7386	Local	1-mile
MHSW	Memorial Hermann Southwest Hospital 7600 Beechnut Houston, TX 77074 713-456-5462	Local	2-miles
MHTM	Memorial Hermann Texas Medical Center 6411 Fannin Houston, TX 77030 832-623-4730	Local	2-miles
SJMC	St. Joseph Medical Center 1401 St. Joseph Parkway Houston, TX 77002 713-356-7936	Local	5-miles
SJDT	St. John’s Medical Center 22101 Moross Road Detroit, MI 48236 313-343-7374	Remote	1345-miles
SJDT	St. John’s Providence 11800 E. Twelve Mile Road Detroit, MI 48236 313-343-7374	Remote	1345-miles

Collection site qualification

New collection sites are qualified following the procedure described in CBB S 001.005.001. The qualification process includes the following elements:

- An administrative agreement for functions such as Institutional Review Board (IRB) review of consent forms.
- A collection agreement and adequate space to perform specified tasks, and storage of supplies and collected product prior to shipment to MDACBB.
- Obtaining information on staff credentials.
- Completion of training on cord blood collection activities.
- Review of the medical record system and request for access.

A collection site initiation checklist is used to document completion of required steps for initiating collections at a new hospital and the Quality Unit performs a site inspection.

Reviewer comment: *Procedures for qualifying new collection sites were not included in the original BLA. The applicant submitted the requested procedure in Amendment 6 (received on 4/16/18). The collection site qualification process is adequate.*

Collection site staff training

At both local and remote collection sites, staff are trained on procedures for donor recruitment, screening and collection of cord blood and other collection related activities. Training procedures are described in SOPs CBB S 001.002.003, CBB S 016.010.003, and CBB S 016.011.003. “Cord blood staff” and “Cord Blood Bank collection staff” are trained to obtain informed consent, perform donor screening, obtain samples for infectious disease testing, perform ex-utero cord blood collection, and prepare the collected products for transport to MDACBB. The training program includes review of relevant SOPs and direct observation of procedures including but not limited to collection and donor screening. Successful completion of at least ^{(b) (4)} procedures under direct observation is required before the procedure can be completed independently. (b) (4) competency is also conducted and documented.

Reviewer comment: *The applicant was asked to explain the difference between “Cord blood staff” and “Cord Blood Bank collection staff” referenced in several SOPs. In Amendment 4 (received on 12/19/17), the applicant explains that “Cord blood staff”, which include a Cord Blood Manager and Cord Blood Assistants, are at remote collection sites. The personnel at the local collection sites are referred to as “Cord Blood Bank collection staff”. Revised SOPs were submitted in Amendment 6.*

At remote collection sites, nursing personnel are trained to obtain informed consent, pre-screen the birth mothers and label collected CBUs when cord blood collection staff is not on-site. Training program for nurses includes review of relevant SOPs, completion of a learning module with at least ^{(b) (4)} test score, and direct observation of activity. (b) (4) competency is also conducted and documented.

OBs and CNMs are trained to perform in-utero cord blood collections. The training program consists of review of SOPs and in-utero collection instruction sheet (CBB I 085.006.003 or CBB I 085.066.002), online training module available on the NMDP website, and direct observation of in-utero collections.

(b) (4) competency is evaluated via completion of the same online training module on the NMDP website or direct observation.

Reviewer comment: *In the initial application, the training programs for local and remote collection sites were not clearly described. In Amendment 6 (received on 4/16/18), the applicant submitted the revised training SOPs and updated BLA section 3.2.P.3.3. The training program is acceptable.*

Donor Recruitment, Pre-Screening and Consent

Criteria for recruitment of the birth mother and informed consent are described in SOPs and policies CBB S 004.007.003, CBB S 016.003.002, CBB P 055.001.006 and BLA section 3.2.P.3.3.1.1 of the application. Birth mothers undergo pre-screening to determine if they are acceptable candidates for donation of their infant's cord blood. Birth mothers are not accepted under any of the following conditions:

- Multiple gestation
- <34 weeks gestation
- <18 years of age
- Known positive for HBV, HCV, HIV, HTLV, syphilis, West Nile virus, or Chagas disease
- Intrauterine fetal demise
- Abnormal pregnancy or known fetal abnormality
- Under the influence of intravenous sedation or mood altering medications
- Women known to speak a language not covered by the IRB
- Actively pushing or in physical distress
- Planning to store cord blood at a private bank
- Deliveries involving surrogacy or adoption

Information regarding the donation process and obtaining an informed consent is provided to the birth mothers that meet the pre-screening criteria.

Reviewer comment: *Revised CBB S 004.007.003 and CBB P 055.001.006 were submitted in Amendment 6. The donor recruitment, pre-screening and informed consent process is acceptable.*

Collection Supplies

Supplies used for cord blood collection are assembled into collection kits for use in the delivery rooms (CBB S 004.003.002 for local collection sites, CBB S 016.005.002 for remote collection sites).

Table 4: Collection Supply List

Component	Description	Specification
Sterile Cord blood Collection Unit, CPD (b) (4)	(b) (4)	<ul style="list-style-type: none"> • Certificate of Analysis indicating product is sterile and conforms to manufacturer specifications • Visual inspection of inner and outer package integrity <p>Sterile Cord Blood Collection Unit, CPD COA</p>
Plasma Transfer Set (b) (4)	(b) (4)	<ul style="list-style-type: none"> • Certificate of Analysis indicating product is sterile and conforms to manufacturer specifications <p>Visual inspection of inner and outer package integrity</p> <p>Plasma Transfer Set COA</p>
Hand sealer and metal clips (b) (4)	(b) (4)	<ul style="list-style-type: none"> • Visual inspection
Zip seal bag	Plastic zip seal bag used as an outer container for the cord blood collection bag for storage and transport post collection.	<ul style="list-style-type: none"> • Visual inspection

The collection kits also include:

- (b) (4)
-
-

For remote collection sites, ex-utero packs containing collection bag label, syringe and needle, and underpad are also prepared. Collection kits are assigned a lot number and an expiration date, which is the earliest expiration date of the kit components and the information is documented.

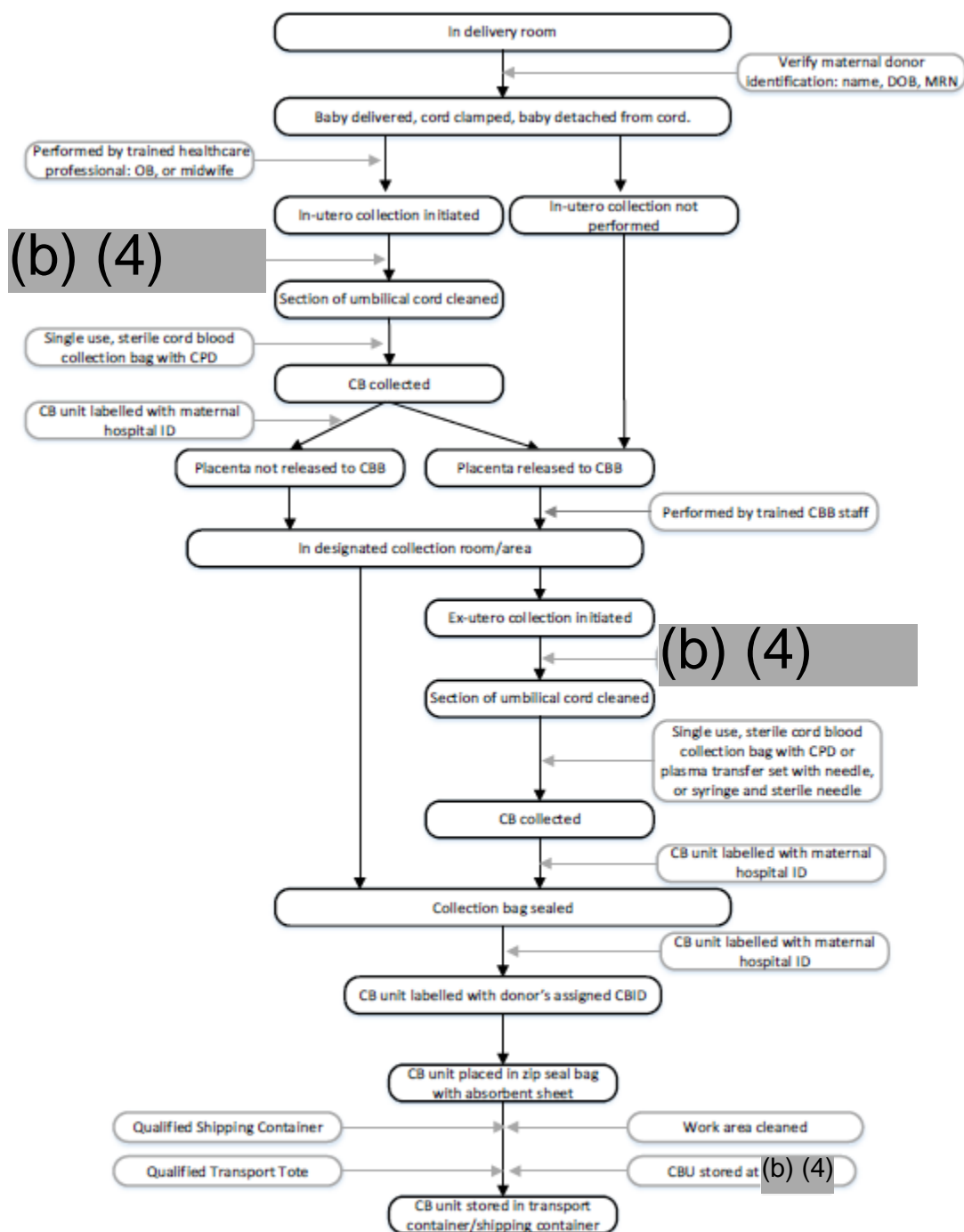
Reviewer comment: *The applicant is using FDA approved cord blood collection bags and FDA cleared standard blood/plasma transfer sets used by blood banks. In the initial application, (b) (4) at remote collection sites were supplied by the hospital and lot numbers of supplies used were not documented. Applicant revised procedure to record lot number and expiration date of reagents used in cord blood collection process. Additionally, (b) (4) have been added to the collection kit. Revised CBB S 016.005.002 was submitted in Amendment 7 (received on 5/14/18). The collection supplies are acceptable.*

Collection procedure and contamination controls

At both local and remote collection sites, cord blood products are collected in uncomplicated vaginal or C-section deliveries, using in-utero and/or ex-utero collection procedures (BLA section 3.2.P.3.3.1.4).

In-utero collections are performed by OBs or CNMs in the delivery room. After the venipuncture site on the cord is disinfected, the needle on the collection bag is aseptically inserted into the cord, and cord blood is collected by gravity flow while mixing with the anticoagulant. Ex-utero collections are performed by trained cord blood staff in dedicated cord blood collection rooms at local collection sites or in the delivery room at the remote collection sites. For ex-utero collection, the placenta is placed in a container labeled with the birth mother's hospital label and transferred to the designated collection area. The placenta is then placed either in a collection stand (at local collection sites) or on an underpad in the designated area in the delivery room (remote collection sites). Ex-utero cord blood collection steps are similar to the in-utero collection method. To maximize the volume of collected cord blood, an in-utero collection may be followed by ex-utero collection depending on cord blood staff availability at the time of delivery. In such cases, the venipuncture site on cord is disinfected and additional cord blood is collected into the same collection bag by using a transfer set or a syringe that is attached to a needle. At remote collection sites, CBUs weighing (b) (4) or were collected (b) (4) hours at the time of preparation for shipment are not shipped to MDACBB and discarded (CBB S 016.006.003). The following flow chart summarizes the collection process:

Figure 1: Cord Blood Collection Flowchart (BLA section 3.2.P.3.3.1.5)



3.2.P.3.3 Description of Manufacturing Process and Process Controls [HPC, Cord Blood, Injectable Suspension]

MDACBB has established the following controls for the collection procedure (CBB S 004.004.003, CBB S 016.008.003, CBB S 016.013.002), to minimize risk of contamination, cross-contamination or mix-ups:

- 1) The birth mother's name and identification number on the hospital wristband is verified against the information on the maternal hospital label and the mother is asked to state her name and date of birth for additional verification.
- 2) Each collector handles one CBU and associated documents at a time.
- 3) Lot number and expiration date of the collection bag is documented on the labor and delivery form (CBB W 081.093.003).
- 4) Single use, sterile collection bag and supplies are used for collection.
- 5) Venipuncture site on the cord is disinfected with (b) (4)
- 6) Collection bag is labeled with the maternal hospital label and the CBID barcode label (see labeling and tracking section for details), and placed inside a zip seal specimen bag.
- 7) Date and time of collection and other relevant information are documented on the cord blood donor labor and delivery form CBB W 081.093.003.
- 8) CBUs are stored and transported in totes that are cleaned before each use.

Reviewer comment: *In the original application, the description of the collection process, including decision to proceed with ex-utero collections, was not clear. Revised SOPs were submitted in Amendment 6. The collection procedure and the established controls are acceptable.*

Storage and Transportation of Collected Cord Blood Units

Post collection, the CBUs and the maternal specimens are stored in transport totes at individual collection sites and transported to the cord blood bank for processing on daily basis (CBB S 007.002.004, CBB S 016.006.003). The transported totes are inspected and cleaned before use. The transport totes contain temperature stabilizing gel packs to maintain the temperature between (b) (4) during storage and transportation. The temperature is monitored using a min/max thermometer. A list of all CBUs and maternal specimens is included in each tote. For local collection sites, the transport totes are picked up by a designated courier service that is trained by MDACBB on transportation logistics (BLA section 3.2.P.3.3.1.7 and SOP CBB S 008.004.002). For the two remote sites in Detroit, which are part of the same hospital system, the transport totes containing the collected CBUs and specimens are transferred from Providence Hospital to St. John Hospital by a local courier service. At St. John Hospital the CBUs, maternal specimens and associated documents are placed in an insulated shipping container (b) (4). A temperature data logger is placed in the shipping container for monitoring the temperature during transit. A maximum of (b) (4) CBUs may be placed in each container and a transport list with the CBU and maternal specimen information is included with each shipment. The containers are shipped to MDACBB via (b) (4) (CBB S 016.004.002). The chain of custody is documented via the transport lists and

courier records (CBB W 081.027.003 for local collection sites; forms for remote collection sites were not submitted).

Reviewer comment: *The storage and transportation procedure are acceptable. Also refer to the shipping validation section.*

Initial Cord Blood Qualification Criteria

Upon receipt, the cord blood unit and the maternal specimens are visually inspected, labels and associated documentation are reviewed and verified for accuracy and completeness. The temperature range from the min/max thermometer is recorded. The CBU is accessioned and submitted to the testing laboratory to determine the CBU weight and time interval since collection. The laboratory re-assesses CBUs from remote collection sites for weight and time interval from collection. The CBU is accepted for processing if the total weight (includes collected CB volume, anticoagulant, and bag) is (b) (4) and received (b) (4) hours from collection. CBUs that meet the volume and time interval acceptance criteria, are transferred to the manufacturing laboratory to remove a sample for pre-processing nucleated cell count determination. CBU is accepted for processing if total nucleated cell count is (b) (4). CBUs not meeting any of these criteria are discarded or used for non-clinical research (CBB S 007.004.006 and BLA section 3.2.P.3.3.2).

Reviewer comment: *According to the information in the original BLA, CBUs that were stored/transported outside the specified temperature range (b) (4) were accepted for processing and banking after review and evaluation by the Quality Unit. The applicant was informed that CBUs that don't meet their storage/transportation specifications are not qualified for licensure.*

Collection Validation

MDACCB's validation plan (CBB V 013.086.002) included validation of procedures related to collection, processing and cryopreservation, testing, storage and shipping. The CBUs included in the validation were collected and transported following established procedures (list of SOPs provided in the validation plan). A total of (b) (4) CBUs that were received from four local collection sites and 1 remote collection site were included in this validation plan and were evaluated for the following pre-processing acceptance criteria:

- Storage and shipping temperature: (b) (4)
- Visual inspection: Collection bag intact with no leakage and labeled, no clots (b) (4)

- Pre-processing: total weight of cord blood unit (CBU) (b) (4) (collected volume, anticoagulant, and bag); Calculated CB volume (b) (4)

All collected CBUs met the storage and shipping temperature, and visual inspection criteria. (b) (4) out of (b) (4) CBUs (89%) met the minimum volume acceptance. (b) (4) of the (b) (4) CBUs (74%) that met the minimum volume requirement also met the pre-processing TNC requirement. Of the (b) (4) CBUs that were processed, (b) (4) CBUs met the post-processing criteria and were tested for sterility. All (b) (4) HPC, Cord Blood units had negative sterility testing results.

Reviewer comment: *The applicant initially submitted a summary of the validation results. In response to information request, the applicant provided the validation plan and detailed results (Amendment 4). For the (b) (4) CBUs that were processed, cryopreserved and tested for sterility, the applicant was asked to identify whether the CBUs were collected by in-utero, ex-utero or the combination method. In Amendment 6, the applicant explains that of the (b) (4) CBUs, (b) (4) were collected using in-utero followed by ex-utero procedure, (b) (4) in-utero only, and (b) (4) ex-utero only. The validation results are acceptable considering that MDACBB either discards or uses the units for non-clinical research if the pre-processing acceptance criteria are not met or the sterility results are positive.*

DONOR ELIGIBILITY DETERMINATION

MDACBB donor eligibility (DE) determination procedures include screening and testing for risks of relevant communicable diseases or disease agents (RCDADs). Donor screening is not performed until the birth mother's informed consent is obtained.

Donor Screening

MDACBB's donor screening includes: 1) donor medical history interview of the birth mother (maternal risk and family medical history questionnaire (CBB W 081.092.003) and associated action guides describing acceptance criteria (CBB I 085.017.002 and CBB I 085.018.001), and 2) review of the maternal and infant donor's relevant medical records looking for clinical and physical evidence of RCDADs (CBB S 004.006.002, CBB S 016.002.001, CBB P 054.001.003, and BLA section 3.2.P.3.3.1.6). The questionnaires are completed via interviews conducted by trained cord blood collection staff. Alternatively, the questionnaires may be completed by the birth mother with a follow-up verbal review by a member of the cord blood collection staff. Trained cord blood collection staff review the birth mother's and infant donor's medical records which includes prenatal history, results of physical examination conducted by hospital healthcare providers, infusion/transfusion and medication history, and the information gathered at the time of labor and delivery. Information and findings are documented on the labor and delivery form CBB W 081.092.003.

Reviewer comment: *On the labor and delivery form, the collection staff documents if conditions such as Meconium staining, Genital infection/sores, Infant digits abnormal, or Chorioamnionitis are identified. The applicant provided the action guide (CBB I 085.001.001, in Amendment 7) that describes which conditions are acceptable or whether additional medical review is needed. The information is acceptable.*

Birth mother and the infant donors are screened for risk factors associated with HIV 1 and 2, HBV, HCV, HTLV I and II, Syphilis, WNV, Sepsis, Vaccinia, TSE, including vCJD, xenotransplantation, and Zika virus. In addition, donors are screened for malaria and other blood borne parasitic diseases (Leishmaniasis, Babesiosis, Chagas disease) which are not currently required by the FDA.

Reviewer comment: *The SOPs submitted in the initial application did not clearly describe the process for donor screening and review of the donor's relevant medical records. Additionally, screening questions for Zika virus risk were included on the medical history questionnaire; however, the SOP did not include information on Zika virus screening. The applicant submitted the revised procedures in Amendment 6.*

Donor Testing

Maternal blood specimens for donor testing are obtained by trained staff within 7 days of infant's birth. Before collection of the specimens, the hospital ID number on the label is verified against the mother's hospital identification armband, and the birth mother is asked to state her name and date of birth. The specimen collection tubes are labeled with the maternal hospital labels at the bedside. The specimen collection date, time, and staff identification are documented on the Maternal blood sample collection form (CBB W 081.096.004). The maternal specimens for testing are not accepted if the birth mother has received (b) (4) of blood, blood components, or (b) (4) within (b) (4) hours, or (b) (4) within (b) (4) of specimen collection. The specimen collection, labeling, preparation and shipment to the testing laboratory are described in SOPs CBB S 004.001.006, CBB S 016.012.003, CBB S 007.011.004). Testing must be initiated within (b) (4) hours of specimen collection.

The infectious disease tests are performed by (b) (4). The testing laboratory is CLIA certified (b) (4) and has AABB accreditation. (b) (4) is registered with the FDA for testing HCT/P donors (FEI # (b) (4)). The test results are transferred electronically to MDACBB.

Birth mothers are tested for the following:

FDA required tests: Anti-HIV 1 and 2 and group O, Anti-HCV, Anti-HBc, Anti-HTLV I and II, HIV/HCV/HBV NAT, HBsAg, WNV NAT, Syphilis, Anti-CMV.

Additional tests not currently required by the FDA: anti-T cruzi.

The testing laboratory performs the tests using FDA-licensed, approved or cleared donor screening tests.

Table 5: Donor Screening Tests

Assay	Trade Name/Manufacturer	Analytical Method	FDA License/STN Number
Anti-HIV-1/HIV-2 +O Human Immunodeficiency Virus Type 1 and 2 (Recombinant and Synthetic Peptides)	(b)	(4)	
HTLV-I/II Antibody to Human T- Lymphotropic types I and II			
HBsAg Antibody to Hepatitis B Surface Antigen			
Anti-HBc Antibody to Hepatitis B Virus Core Antigen			
Anti-HCV Antibody to Hepatitis C Virus Encoded Antigen (Recombinant c22-3, c200, and NS5)			
Anti-T Cruzi Chagas Trypanosoma cruzi Whole Cell Lysate Antigen			
West Nile Virus			
CMV Antibody to Cytomegalovirus			
HIV-1 Presence of human immunodeficiency virus type I (HIV-1) RNA			
HCV Presence of hepatitis C virus RNA			
HBV Presence of hepatitis B virus DNA			
TPA Qualitative detection of IgG and IgM antibodies to Treponema pallidum			

MDACBB does not store HPC, Cord Blood from birth mothers who test positive or reactive for the above donor screening tests, except for CMV and Hepatitis B core antibody. MDACBB determines donors who test reactive for Hepatitis B core antibody as ineligible and HPC, Cord Blood from such donors are stored

and made available for use under an IND, if there is a documented urgent medical need. CMV results are reported to the transplant center.

MDACBB performs supplemental and confirmatory testing for positive infectious disease test results (except for CMV) for mandatory reporting to State agencies, notification to the birth mother's physician and infant donor's pediatrician, if required by the collection hospital's IRB. The notifications are sent via certified courier or secure fax line, as requested by State agencies and/or medical provider (BLA section 3.2.P.3.3.1.8 and CBB S 002.017.005).

Reviewer comment: *In Amendment 1 (received on 10/11/17), the applicant submitted the revised CBB S 002.017.005 that clearly states the results of supplemental/confirmatory testing do not override the initial donor screening test results for donor eligibility determination purposes.*

Final Donor Eligibility Determination

HPC, Cord Blood are maintained in quarantine until records associated with the collection, manufacturing, testing results, and storage are reviewed and the DE determination is completed. The donor screening and other collection documentation are uploaded into the MDACBB's (b) (4) system that is linked to a review management system called (b) (4). MDACBB uses a multi-step process for making the DE determination. The results of donor screening and testing are first reviewed by a trained CBB staff who assigns the donor eligibility status. Risk factor findings are flagged for additional clinical review by the medical director or designee. The DE determination is reviewed and signed-off by the medical director or designee before the unit is listed on the registry (CBB S 008.002.004).

MDACBB determines the donor to be eligible if the donor screening does not identify any risk factors for RCDADs and all the infectious disease test results are negative or non-reactive, except for CMV (CMV results are reported).

MDACBB stores HPC, Cord Blood units from certain ineligible donors (donors with reactive test results for Hepatitis B core antibody or travel related risks). Such units are listed with the donor registry and made available under an IND. Units from donors for whom the DE determination is not complete are not listed with the donor registry (CBB S 008.002.004).

MDACBB contacts the birth mother to obtain follow-up information related to current health of the infant donor and immediate family members when a request is received for confirmatory testing or before distribution of the unit if the last follow is longer than 6 months. The donor registry is notified if the birth mother cannot be reached for obtaining new health information (CBB S 006.001.002). At time of distribution, a summary of records that includes the required information (21 CFR 1271.55) accompanies the HPC, Cord Blood.

Reviewer comment: *The donor screening, testing, and DE determination procedures are acceptable and in compliance with 21 CFR part 1271.*

Donor Tracking and Labeling

The applicant is using ISBT 128 identification and labeling system in lieu of the NDC.

MDACBB ISBT 128 facility code: W2263

MDACBB ISBT 128 product code: S1393

Labeling of Collected Cord Blood and Maternal Samples

MDACBB utilizes the ISBT 128 system for assigning a distinct identification code to the cord blood unit and maternal blood samples for donor testing. The distinct identification code is the ISBT Donation Identification Number (DIN). The DIN is presented in barcode and eye-readable form. The process for label management is described in CBB S 002.020 Barcode Label Management for Collection.

The ISBT Donation Identification Number (DIN) consists of 13 characters, starting with a “W” followed by 12 digits. The first five characters is the facility identification number (FIN). The next two characters represent the year of collection. The last six characters are numbered sequentially from 000001 to 999999, enabling 999,999 unique product identifiers per year.

Example: W226316012345 = W2263 (MDACBB facility code for HPC, Cord Blood) + 16 (year 2016) + 012345 (sequential numbers, referred to as CBID).

The DIN assigned to the maternal specimens has a different ISBT 128 FIN.

Example:

W226316012345 = DIN assigned to the cord blood unit

W367716012345 = corresponding DIN assigned to maternal blood samples

Note: DINs starting with “W3677” prefix are assigned to maternal blood samples

ISBT product and sample labels are controlled at MDACBB by the (b) (4) database application. For collection activities, a set of pre-printed barcode labels (total of (b) (4) individual labels) are generated at MDACBB and are distributed to the collection sites. Each individual label includes the CBID (6 digits, presented in barcode and eye-readable form) which include the label description to indicate where the label will be affixed. A CBID barcode label is placed on the cord blood collection bag and all associated forms. The set also includes the DIN labels for the maternal blood samples. When the cord blood products are received and accessioned at MDACBB for processing, barcode readers are used to scan the

CBID label affixed to the collection bag or associated documents. All subsequent labeling is generated during processing by scanning the CBID.

Reviewer comment: *In the initial application, the description of the process for management of labels and controls were unclear. The applicant submitted a revised SOP that adequately describes the process (Amendment 6, CBB S 002.020.003).*

Tracking

MDACBB utilizes ISBT 128 Donation Identification Number (DIN) for tracking cord blood units and linking with maternal blood samples. The informed consent form is used to maintain linkage between the birth mother and the donated CBU. At the collection sites, the maternal hospital label, with the birth mother's name, date of birth, and medical record number, is initially used to label all documents, samples, and product collection bag. The confidential donor information is maintained in a secured filing system with access limited to authorized personnel. The CBID is used for labeling all subsequent documentation and generating the DIN labels. The ISBT 128 DIN is included on the final HPC, Cord Blood container and all documentation for registry listing and shipment to the transplant centers. (CBB P 054.002.004, CBB S 004.007.003).

Reviewer comment: *The tracking process is acceptable.*

CORD BLOOD PROCESSING

Cord Blood Receipt and Accessioning

Cord blood units are received at the Cord Blood Bank daily from the local and remote collection sites. Units are shipped in transport totes (local collection sites) or shipping containers (remote collection sites). Trained laboratory personnel are responsible for receiving collected cord blood and maternal samples at the processing facility. Upon receipt, the units and associated maternal blood samples are removed from the shipment container, inspected, and reconciled against the transport list. The units are then put into sealable plastic containers and transferred into the accessioning room in the clean room via the interlocking pass through box.

In the accessioning room, each cord blood is evaluated for integrity/appearance and checked into the cord blood information system (b) (4) computer. The barcoded cord blood ID (CBID) assigned/affixed to the unit during collection is scanned into the system; the collection date and time on the label are also input in the (b) (4). Thereafter, all subsequent labeling is generated by scanning the CBID affixed on the collection bag.

After accessioning, each cord blood unit is weighed to determine the volume collected. Units are released for processing, if the Actual Cord Blood volume (unit volume excluding anticoagulant) is (b) (4) and time from collection is (b) (4) hours post collection. Cord blood units which do not meet the specification for Actual Cord Blood volume and time from collection are discarded. CBUs meeting the these specifications are transferred through the pass through box to the manufacturing lab for pre-processing sampling to assess total nucleated cell counts (TNC).

In the manufacturing lab, (b) (4) sample of cord blood is removed from each CBU using a (b) (4) syringe and sterile connection. The sample aliquots are passed into the testing laboratory where a pre-processing cell counts is performed: each unit is assessed for total nucleated cell count which includes nucleated red blood cell count. CBUs meeting all pre-processing criteria listed in Table 6 below are released for processing. These units are placed into the manufacturing box.

Table 6: Cord Blood Specification- Release for Processing

Assay	Sample	Analytical Method	Specification
Time from Collection	N/A	N/A	(b) (4) hours post collection
Bag Appearance	CBU ¹	Visual inspection	Bag intact (no visible cracks or other damage)
Cord Blood Appearance	CBU	Visual inspection	No visible clots (b) (4) size, foreign material or contamination
Actual Cord Blood Volume	CBU	Weight	(b) (4)
Total Nucleated Cell Count (TNC)	Pre-process sample from CBU	(b) (4)	(b) (4)
Nucleated red blood cells	Pre-process sample from CBU	(b) (4)	(b) (4)

CBU¹ = Cord Blood Unit

Cord Blood Processing Using (b) (4) Device

Overview

A (b) (4) method of processing cord blood is used under this BLA, an (b) (4) method using (b) (4) device. CBUs meeting the pre-processing criteria are segregated in individual work bins with corresponding supplies for processing. Procedural steps are documented concurrently under 'Procedure Record' tab in the (b) (4) computer using the worksheet, CBB W 081.274: Processing Times Log.

(b) (4)

(b) (4)

[Redacted]

Processing Details

Addition of (b) (4)

After accessioning, cord blood units (CBU) meeting the pre-processing TNC criteria are prepared for processing in the manufacturing lab. Hydroxyethyl starch (HES), in the amount of (b) (4) the volume of cord blood unit, is added to each CBU to a final concentration of (b) (4) HES. The required volume of HES is (b) (4)

[Redacted]

(b) (4) *Volume Reduction*

(b) (4)

[Redacted]

(b) (4)

(b) (4)

(b) (4)

[Redacted]

(b) (4)

Post-Processing of HPC, Cord Blood

(b) (4)

Table 8: Cord Blood Specifications- Release for Cryopreservation

Assay	Sample	Analytical Method	Specification
Time from Collection	N/A	N/A	Cryopreserved within (b) (4) hours of collection
Bag Appearance	Cryobag containing buffy coat enriched CBU	Visual inspection	Bag intact (no visible cracks, leaks or other damage)
CB Appearance	Cryobag containing buffy coat enriched CBU	Visual inspection	No visible clots (b) (4) size, foreign material or contamination
Buffy Coat Volume	Cryobag containing buffy coat enriched CBU	Volume reported by (b) (4) device	(b) (4)
Total Nucleated Cell Count	Post-process sample of CBU	(b) (4)	(b) (4)
Nucleated red blood cells	Post-process sample of CBU	(b) (4)	(b) (4)
Hematocrit	Post-process sample of CBU	(b) (4)	(b) (4)

Note: During the pre-licensure inspection we observed that the firm was creating 4 segments instead of the three reported in the original submission. The four segments would allow the retention of a true sample which is representative of the HPC, Cord Blood product. We advised them to send this change in an amendment to the original application (submitted in amendment 7).

Cryopreservation and Storage of HPC, Cord Blood (SOP 007.003.007)

HPC, Cord Blood units meeting the post-processing specifications and the freezing canister are kept at (b) (4) for a minimum of (b) (4) before proceeding to cryopreservation. The cryoprotectant, Dimethyl sulfoxide (DMSO)/Dextran 40 is added to a final concentration of 10% DMSO and 1% Dextran 40. (b) (4) syringe containing (b) (4) cryoprotectant (b) (4) DMSO (b) (4) Dextran 40 in 0.9% Sodium Chloride solution stock) kept cool at (b) (4), is connected to the buffy coat bag (cryobag) fill line using sterile connect device. The Cryobag is installed on the (b) (4) mixing/cooling device (b) (4) which is maintained at (b) (4). The barcoded CBID is scanned into the device for traceability. The (b) (4) DMSO/Dextran is then added over a (b) (4) period or greater with mixing at a temperature range of (b) (4). Once DMSO addition is complete, freezing must occur within (b) (4) the product must be kept cold and handled as little as possible. The time between the beginning of DMSO addition and the start of freezing should be no more than (b) (4).

Excess air is removed from the freezing bag using the attached (b) (4) and (b) (4) equal segments are created and labeled; the bridge between the two compartments of the freezer bag containing the HPC, Cord Blood is heat-sealed to create 80% /20% fractions.

Overwrapping of the HPC, Cord Blood

The sealed bag and accompanying segments are sealed in the (b) (4) overwrap sleeve and placed inside the labeled pre-cooled storage canister. A second technologist verifies the CBID on the freeze bag and with the CBID on the storage canister. The canister containing the HPC, Cord Blood is then transferred to the (b) (4) system for controlled rate freezing.

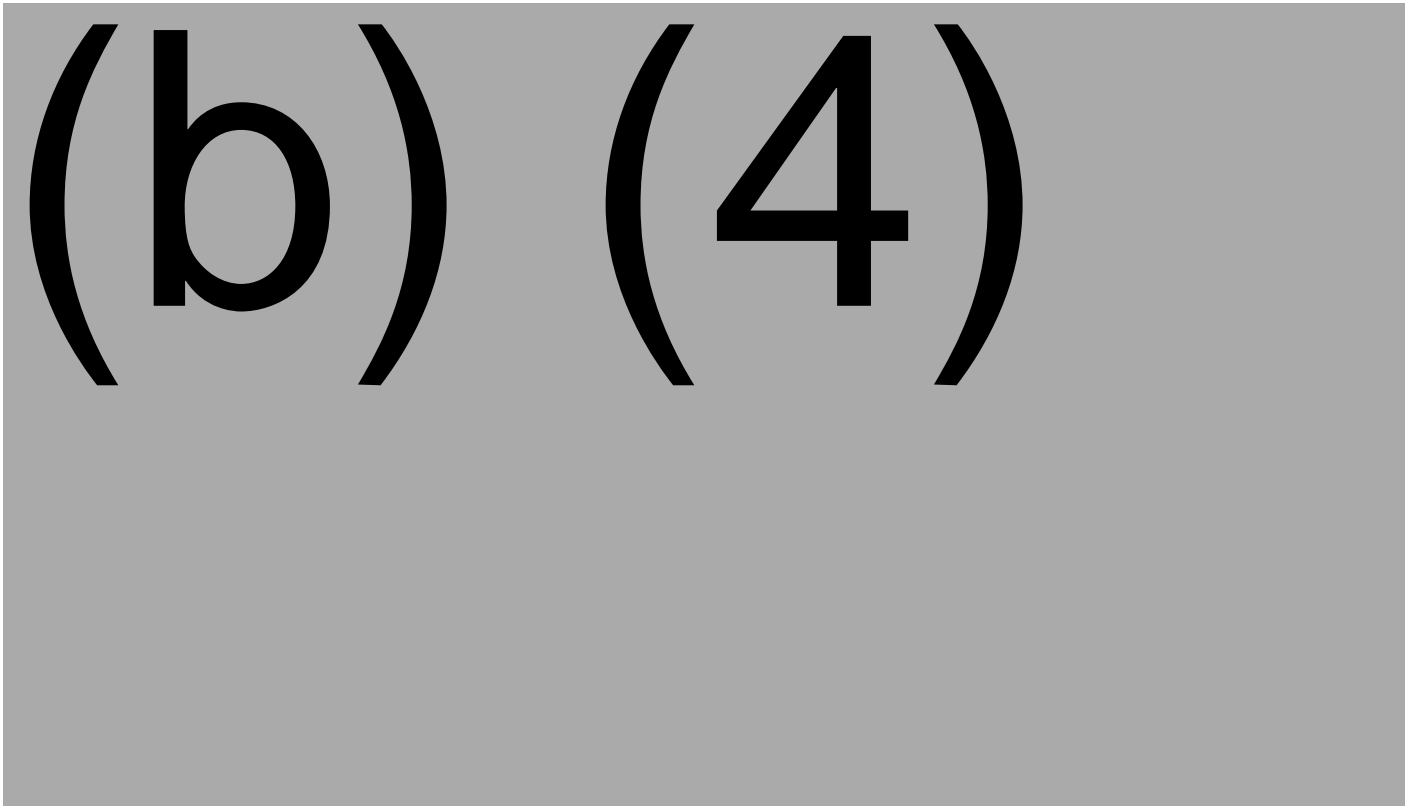
Controlled Rate Freezing and Storage

The HPC, Cord Blood is kept cool after addition of cryoprotectant. Freezing must be initiated within (b) (4) of addition of cryoprotectant. The canister containing the HPC, Cord Blood is placed into the controlled-rate freezer and the freezing process is initiated. (b) (4) HPC, Cord Blood products can be frozen in the same freezer at a time. The freezing profile used to freeze the HPC, Cord Blood, consists of defined cooling rates for the specimen while it is in a liquid state (pre-freeze) and after it has frozen (post-freeze).

When the cord blood unit reaches (b) (4), the (b) (4) automatically moves the unit into long term storage in liquid nitrogen. At the end of freezing, the storage location and a graph of the freezing profile are automatically printed out. Cord blood units that fail to reach (b) (4) are discarded.

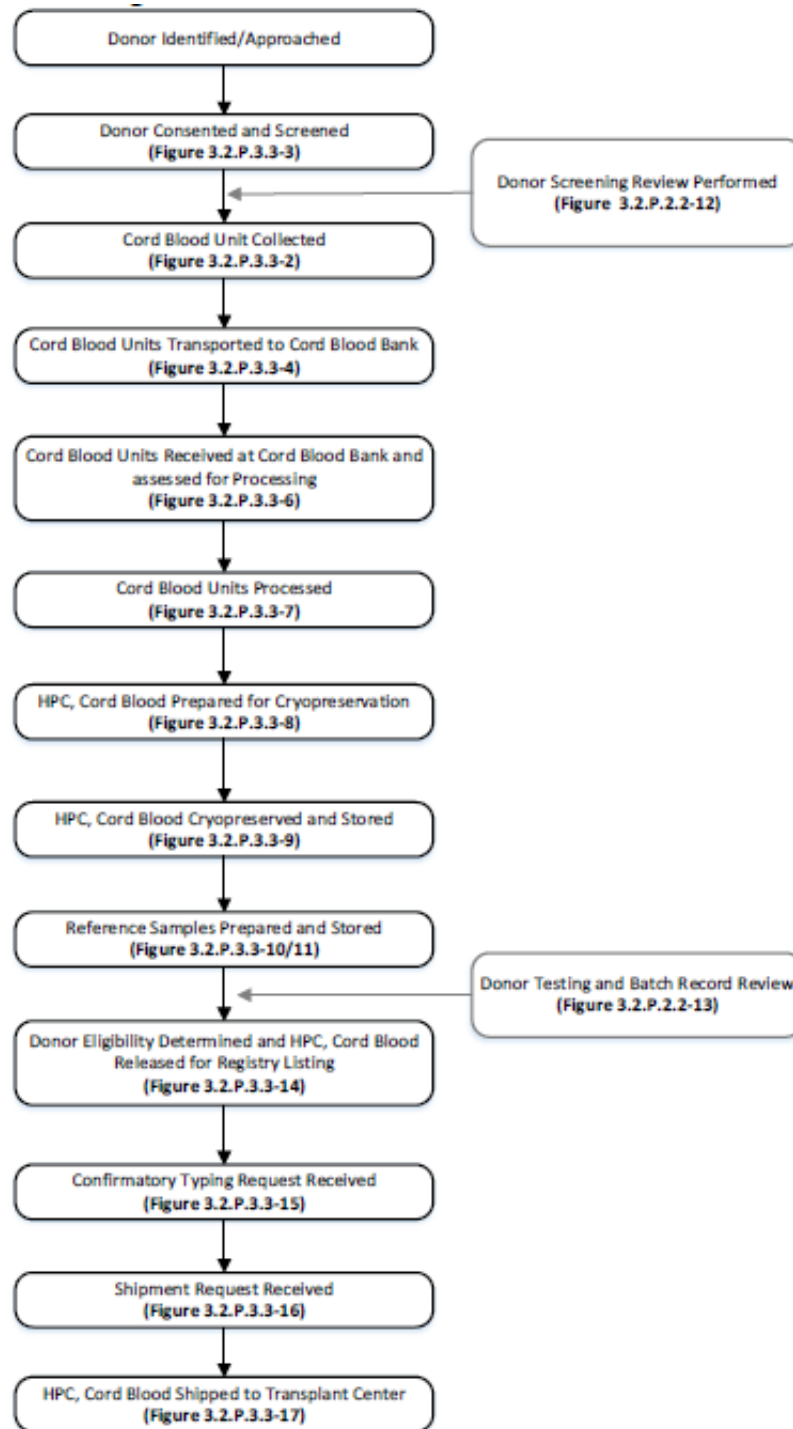
The graph below in Figure 2 illustrates the freezing protocol during controlled rate freezing.

Figure 2: Freezing Protocol for Controlled Rate Freezing :



Note: The (b) (4) system is an (b) (4) freezer that is used to cryopreserve and store HPC, Cord Blood units. (b) (4), has a Drug Master File for this instrument under MF (b) (4). A cross-reference authorization from (b) (4), for the (b) (4) System for MF (b) (4) is provided in amendment 5 to the BLA.

Figure 3: Overview of HPC, Cord Blood Manufacturing Process



2.3.P.3 Manufacture [HPC, Cord Blood, Injectable Suspension]

CORD BLOOD PROCESSING VALIDATION

Protocol Number SOP V 013.086.002 was followed for the process validation study to demonstrate a controlled collection, processing, cryopreservation, and thawing of HPC, Cord Blood units. The validation results were reported.

Description of Protocol

The protocol (SOP V 013.086.002) outlined the procedures and acceptance criteria for the validation. A total of (b) (4) cord blood units collected on a (b) (4) were processed for this validation study. The units were collected from 5 collection sites (four local and one remote), processed, tested and stored according to current SOPs.

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 were downloaded prior to processing to ensure that the (b) (4) range was maintained during transport. Cord Blood units that met the shipping temperature criteria, visual inspection criteria, were pre-processed for total weight of cord blood unit (b) (4) (cord blood + anticoagulant + bag), a calculated minimum volume (b) (4) nucleated red cell count (NRBC: (b) (4) and a total nucleated cell count (TNC: (b) (4) Cord blood units meeting the pre-processing acceptance criteria listed in Table below were further processed by volume reduction on the (b) (4) device. Units that were processed on the (b) (4) device were tested for sterility and also, HLA typed.

Pre-Specified Criteria

Table 1 below contains the pre-processing criteria that the collected cord blood has to meet in order to be processed

Table 9: Pre-Processing Acceptance Criteria

Parameter	Acceptance Criteria
Shipping Temperature	Minimum/Maximum temperature must be within (b) (4) (b) (4) range, according to shipping data logger.
CBU Condition (Visual Inspection)	Collection bags must be received intact, labelled, and not leaking
Visual Inspection	No clots greater than the size of a (b) (4) are present in the CBU bag (surface area, as clots may be irregular)
CBU Weight Verification (Measured)	Total weight of CBU is (b) (4) (CB, anticoagulant, and bag)
CBU Volume Verification (Calculated)	CBU volume must be (b) (4)
Total Nucleated Cell Count (TNC)	CBU pre-processing TNC must be (b) (4) and NRBC (b) (4) of TNC

Cord blood units meeting the pre-processing criteria moved on to be processed/volume reduced on the (b) (4) device. Table 2 lists the post-processing acceptance criteria that were met in order for the unit to be cryopreserved.

Table 10: Post-Processing Acceptance Criteria

Parameter	Expected Results
Cell Recovery	(b) (4)
Cell Dose	
Viability	
CD34 Analysis	
Colony Forming Unit Assay	
Aerobic and Anaerobic Sterility*	

* Results not available prior to cryopreservation

Cord blood units meeting the post-processing acceptance criteria in Table 2 were cryopreserved as per CBB S 007.003 (Cryopreservation and Storage of Cord Blood Units Using the (b) (4)).

Post-Thaw Validation

To determine whether frozen HPC, Cord Blood units met the post-thaw criteria, (b) (4) of the cryopreserved HPC, Cord Blood units were thawed (b) (4) hours post freezing according to SOP CBB S 007.017 (Wash of Cryopreserved HPC Cord Blood on (b) (4) Device) and tested as outlined in Table 3 below. Confirmatory HLA typing testing was conducted on a contiguously attached segment on (b) (4) HPC, Cord Blood units.

Table 11: Post-Wash Acceptance Criteria

Parameter	Expected Results
Cell Recovery	(b) (4)
Viability	
CD34 Analysis	
Colony Forming Unit Assay	
Aerobic and Anaerobic Sterility	

Results

Pre- and Post-Processing

The transport temperatures for all the collected (b) (4) CBU were all within the specified range of (b) (4) . Of the (b) (4) cord blood units collected, (b) (4) met the specification for minimum volume, time from

collection and transport temperature, and advanced on to pre-processing testing. (b) (4) out of the (b) (4) units met the pre-processing TNC specification and moved on to be volume reduced on the (b) (4) units processed met the post-processing criteria (b) (4) units did not meet the minimum TNC criterion) and were sampled for sterility testing. These (b) (4) HPC, Cord Blood units were cryopreserved and frozen stored/banked. (b) (4) units out of the (b) (4) HPC, Cord Blood units banked were thawed after (b) (4) hours for post-thaw analysis.

Post-Thaw Analysis

Results of the post-thaw analysis of the (b) (4) cryopreserved HPC, Cord Blood units thawed (b) (4) hours after freezing are summarized in Table 15 below. The cryopreserved HPC Cord Blood units used for this validation were washed on (b) (4) Device. The test results on the HPC, Cord Blood characterization post-thaw and wash, as well as the sterility test results are summarized in Table below. All established criteria were met in the validation.

Table 12: HPC, Cord Blood Thaw and Wash Data

(b) (4)

Note: This table was re-created from the applicant's data.

Confirmatory HLA-typing was performed on (b) (4) used for the post-thaw analysis; initial HLA-typing results were confirmed.

Reviewer comment: The validation performed and the results obtained are adequate.

SHIPPING AND SHIPPING VALIDATION

Shipping From Collection Site to Processing Facility

MD Anderson Cord Blood Center receives cord blood units (CBUs) from 7 collection sites/partners. These collection sites are in Houston, Texas (5 sites) and Detroit, Michigan (2 sites).

Local Site Storage and Transport

Cord blood units are stored in a temperature monitored transport tote. Transport totes contain temperature stabilizing gel packs used to buffer the contents of the tote from changes in ambient temperature. Prior to use, totes are inspected and cleaned as per CBB W 081.084.005). Cord blood units and maternal blood samples are packed to ensure that product viability and integrity are maintained while ensuring the safety of Cord Blood Bank personnel (CBB S 007.002.003). Each shipment is monitored using a calibrated min/max thermometer used to evaluate whether the samples were maintained between (b) (4) for the duration of the storage and transport period. A transport list cataloguing all specimens within the transport tote is included with each shipment (W 081.027.002). Local transport is performed by a courier service, (b) (4). The courier travels to up to 5 collection sites consecutively and delivers transport totes and secured document file boxes to the Cord Blood Bank within (b) (4) of initial pick-up (CBB S 008.004.002). Secured transport totes and secured file boxes are conveyed in the climate controlled, main cabin of a motor vehicle operated by the courier.

Remote Site Storage and Transport

The two remote collection sites are in the Detroit, Michigan area, approximately 25 miles apart, and are members of the same hospital system. Prior to packaging cord blood units and maternal blood samples for shipment, shipping containers are cleaned and inspected for integrity and proper labelling (CBB S 016.004.002). CBUs are shipped in the (b) (4) containers. CBUs shipped from remote collection sites to the Cord Blood Bank are monitored by calibrated (b) (4) temperature data loggers to evaluate whether the samples were maintained between (b) (4) for the duration of the shipping period (CBB S 016.007.003). A transport list cataloguing all specimens within the shipping container is included with each shipment. (W 081.027.002) along with the cleaning log (W 081.084.005). Cleaning and inspection of the shipping container and identification of the temperature loggers are recorded on the log. Immediately prior to shipment, the shipping containers are sealed. Shipping of transport totes from the remote collection site to the Cord Blood Bank is performed by (b) (4), with "Overnight First AM" service. (b) (4) collects shipping containers from St. John's Medical Center-Detroit, MI and ships to the Cord Blood Bank via (b) (4) for a total distance of approximately 1,345 miles. Shipping times range from (b) (4) hours. Tracking information is provided by (b) (4) for each shipment with record of pickup, transit, and delivery times throughout the shipping process.

Validation of Shipping From Collection Site to Processing Facility

Validation studies were performed by the sponsor to demonstrate that the transport tote can maintain an internal tote temperature within the specified (b) (4) during transport along the longest transport route (between all local collection sites to the Cord Blood Bank) for cord blood units and maternal blood samples. The studies were performed using (b) (4) simulated CBUs and Maternal samples. The transport totes were qualified to maintain the specified temperature of (b) (4) when maintained at (b) (4) for about (b) (4). Similarly, it was shown that the transport

totes were able to maintain the specified temperature for (b) (4) hours when exposed to temperatures below (b) (4) and higher than (b) (4). The CBU s that fall outside the specified temperature range are rejected. The Min-Max thermometer were used for the local sites; these thermometers are qualified and maintained as per (CBB W 081. 003.002). The (b) (4) temperature loggers were used with the transport totes for the remote sites, these data loggers were qualified and validated as per (CBB S 011.022.002).

Reviewer Comment: During the review of the original submission, the sponsor was requested to provide following information:

- a. Actual shipping times and expected conditions from the collections sites to the manufacturing site.
- b. Identify the couriers and air-flight carriers used during the local and long distance transportation.
- c. Please clarify if the temperature probes are used to monitor in both short distance and long distance transportation. Also, provide information on the make and model of the temperature probe along with its validation data.

Sponsor's Response: In response to above query, sponsor provided responses to the requested information as an amendment 3 dated 10/27/2017. The sponsor provided the validation of transport totes demonstrating they maintain the specified temperatures for the duration of the shipments. The information was provided on the couriers used. In, addition information was provided on the temperature probes.

Reviewer comment: The validation and information provided was found to be adequate.

Shipping of HPC, Cord Blood to Transplant Center

MD Anderson Cord Blood Center ships the CBUs to the transplant centers worldwide. The CBUs are shipped using the (b) (4) that maintains (-150°C or colder) temperatures (CBB S 011.017.003). The (b) (4) is designed for the safe transportation of biological products and samples at cryogenic temperatures. It employs a (b) (4) that retains liquid nitrogen. The samples to be transported are held in the (b) (4) of the liquid nitrogen during shipment. The outer walls of the shipper contain a vacuum seal that allows minimal temperature change due to external environment. The (b) (4) fits into a (b) (4) shipping carton, designed to protect the shipper in transit. The shipper can hold temperature at -150°C for more than (b) (4).

Once a cord blood unit is selected by a transplant center, National Marrow Donor Program (NMDP) assigns a case manager and the details of the ordering and shipment (unit ID and sample requests, shipment date, and transportation courier) of the CBU. On the day of shipment, the shipment packet is generated and reviewed during release for distribution by Quality Assurance provided by a trained lab

personnel. Working one unit at a time, all applicable identifiers (CBID, ISBT ID, NMDP ID, Recipient Name, and Recipient ID) on all documents that accompany the HPC, Cord Blood unit are verified. The excess liquid nitrogen (b) (4) the shipper is removed from dry shipper and the data logger is configured with shipment specific information to maintain linkage between the logger and HPC, Cord Blood unit being shipped. Data logging is initiated and the internal temperature of the dry shipper is confirmed to be $\leq -150^{\circ}\text{C}$. Pre-loading verification checks, including verification of identifiers on completed documents, verification of active temperature logging, and confirmation that the internal temperature of the dry shipper is $\leq -150^{\circ}\text{C}$, are completed by a second team member. Removal of the HPC, Cord Blood unit from storage in the (b) (4) is initiated by scanning the barcoded ISBT unit identifier located on the shipment report provided with the shipment packet. HPC, Cord Blood units retrieved from storage are immediately transferred into a temperature monitored vessel capable of maintaining the product temperature at $\leq -150^{\circ}\text{C}$ (S 011.043.001). The identity of each unit removed from storage is visually confirmed by (b) (4) trained laboratory technicians and loaded into the prepared liquid nitrogen dry shipper. After loading, the inner lid of the dry shipper is secured with a tie tag bearing the unit identifiers. The shipment packet containing the product insert and cord blood unit summary of records is secured inside the outer shell of the shipper. Post-loading verification checks, consisting of verification of unit identifiers on the shipment packet, tie tag securing the inner lid, and tie tag securing the outer lid, are all completed by a (b) (4) team member. HPC, Cord Blood units packed for shipment are released to couriers for shipment to transplant center only upon verification of the shipment tracking number at the time of pick up (CBB S 008.003.003)

Validation of Dry Shippers

Dry shippers were initially validated for (b) (4) (CBB 011.017-002). This validation included steps to establish, maintain, and operate the (b) (4) Dry Shippers.

Validation is performed at least (b) (4) to verify shipper continues to conform to all specifications tested by the test case. (b) (4) qualification follows the steps of the initial material qualification. All dry shippers must be qualified and maintain the minimum validated shipping interval (MVSII) for the manufacturer/model being qualified before use.

Table 13: Dry Shipper Criteria

(b) (4)

If dry shipper is new to inventory or has been repaired, (b) (4) performance qualification runs must be performed and documented prior to release for use. If dry shipper is due for (b) (4) quality control, (b) (4) performance (b) (4) must be performed and documented prior to release for use label unqualified shippers with an “out of service” label.

The sponsor has submitted the data on the actual shipments demonstrating that the shippers were able to maintain specified temperature of -150°C for the duration of the shipment. The typical time for the above shipments was (b) (4)

Reviewer’s Comment: *The dry shipper validation data was found to be adequate to support the receipt of the CBUs with the intact container closure and at the recommended temperature ($\leq -150^{\circ}\text{C}$).*

THAWING AND CRYOPROTECTANT REMOVAL: VALIDATION SUMMARY

The applicant describes two cryoprotectant removal/wash procedures and their validations for the thawed HPC, Cord Blood unit: a (b) (4) wash, and (b) (4) device wash procedures. The (b) (4) wash procedural instructions will be included in the prescribing information in “Instructions for Preparation for Infusion”, which accompanies the shipped HPC, Cord Blood to the clinical site/transplant center. The (b) (4) wash procedure will be used in-house for washing HPC, Cord Blood units that will be used in the (b) (4) Stability program to (b) (4) of the product.

Description of Thawing Procedure

SOP S 007.019 (Thawing or Cryopreserved Cord Blood Units) is followed to thaw HPC, Cord Blood units prior to washing by either the (b) (4) wash methodologies.

(b) (4)

(b) (4) Wash Procedure (SOP S 007.025.001)

Description of Procedure

(b) (4)

(b) (4)

(b) (4)

Validation of (b) (4) Wash Procedure (SOP V 013.095.001)

(b) (4)

(b) (4)

(b) (4)

Results: All the HPC, Cord Blood units met the post-thaw and wash pre-specified criteria. The results are summarized in Table 15 below.

Table 15: Post-Wash Outcome Data

(b) (4)

Reviewer comment: The post wash stability was not addressed in this validation, i.e. establishing holding conditions (holding temperature and time duration to hold) after wash. This information was requested in a telecon to the applicant. In an amendment to the BLA via email on March 16, 2016, the post wash stability was addressed (documented below).

Expiration and Holding Conditions for (b) (4) Washed HPC, Cord Blood

The stability (holding time temperature after wash) of the HPC, Cord Blood unit post-thaw and wash was addressed in an amendment 7, submitted via email on March 16, 2018. (b) (4)

Table 16: Acceptance Criteria for (b) (4) Washed HPC, Cord Blood

(b) (4)

The applicant explains that based on their experience with the (b) (4) wash procedure, which maintained product stability at both (b) (4), they elected to eliminate some time points and demonstrate stability beyond (b) (4). Hence, (b) (4) time points were evaluated. The HPC, Cord Blood unit, after thaw was initially sampled for analysis (time (b) (4) then (b) (4)). Samples were taken and evaluated at (b) (4).

The results are summarized in the tables below (Tables 17,18, 19, and 20) below.

Table 19: CD34+ Viability

(b) (4)


Table 20: CFU Assay Results

(b) (4)


(b) (4) Wash Procedure (SOP S 007.017.003)

Description of Procedure

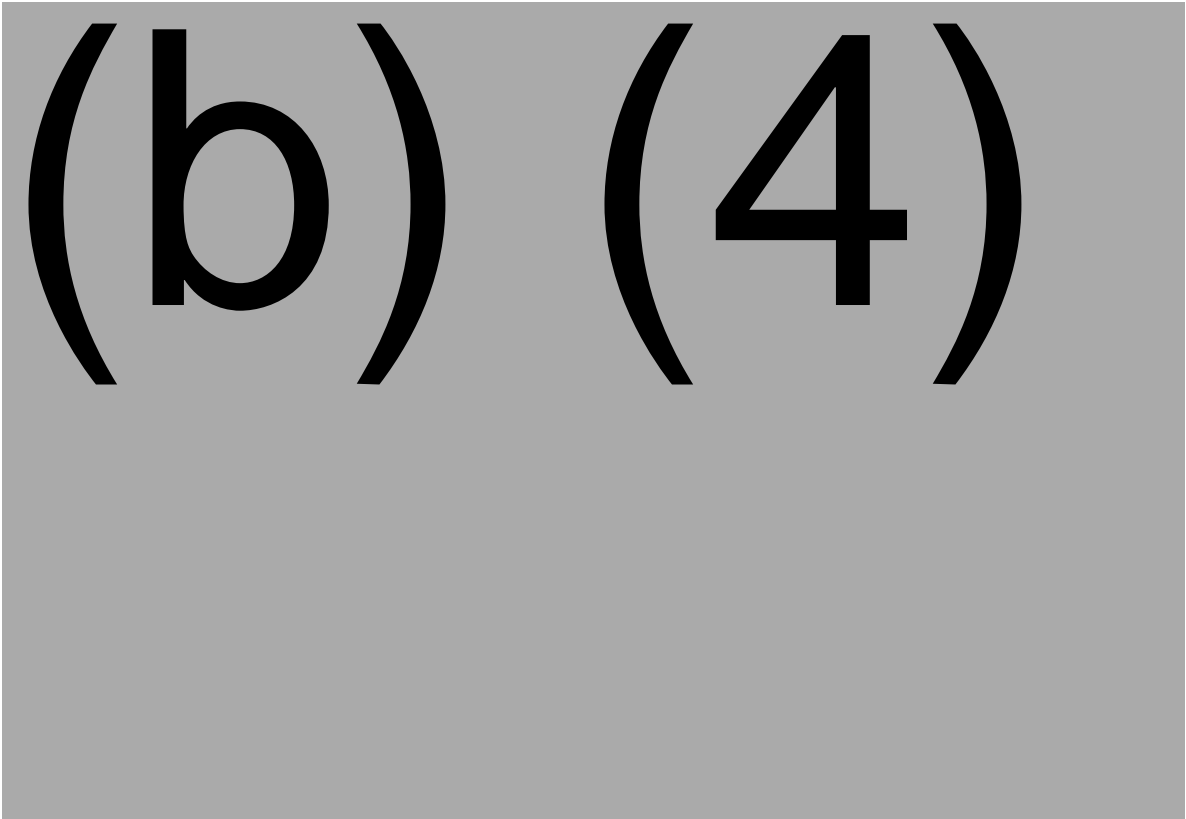
(b) (4)



(b) (4)




(b) (4)



(b) (4)



(b) (4)



(b) (4)

(b) (4)

Validation of (b) (4) Wash Procedure

(b) (4)

(b) (4)

(b) (4)

Table 21: Acceptance Criteria

(b) (4)

Reviewer comment: The (b) (4) wash validation is adequate. This wash procedure will be used for the (b) (4) stability study to (b) (4)

Expiration and Holding Conditions for (b) (4) Washed HPC, Cord Blood

This validation was submitted in response to a December 13, 2017 information request; the applicant was asked to establish the holding conditions and stability of the (b) (4) washed cord blood unit. In other words, how long and under what conditions can the (b) (4) washed cord blood unit be held until the unit is transplanted. The (b) (4) wash procedure was validated, but the applicant did not provide data to establish holding conditions and stability for the washed product. The study described in this section was performed to support the holding condition and time limit within which the washed product may be used.

For this study, (b) (4)



The sampling scheme is listed in the Table 25 below.

Figure 5: Flow Chart of Sampling for Expiration and Holding Studies

(b) (4)

Table 22: Sampling Times for Expiration and Holding Studies

(b) (4)

Test results had to meet the acceptance criteria listed in the Table 23 below. The time point after which the test results fail the expected criteria is established as the maximum time limit to hold the thawed product at that temperature or condition.

Table 23: Quality Control Test Release- Expected Results

(b) (4)

Results

(b) (4)

Conclusion

All the parameters assayed met their pre-specified criteria for the (b) (4) time points studied. The applicant, however, chose the (b) (4) time point as the preferred holding time for both (b) (4) conditions.

Reviewer comment: The holding condition for the washed product will be established at (b) (4) for (b) (4) temperature conditions.

STABILITY PROGRAM FOR EXPIRATION DATING

The applicant has a stability program in place to assess the stability of the cryopreserved HPC, Cord Blood in support of the storage conditions and to monitor and (b) (4). The protocol is described in document S 002.022.003, titled: *Stability Program*. A report on the initial stability testing executed in 2016 is contained in document S 002.022.001, titled: *Summary Report: Stability Program*, which summarized the stability testing results in support of the current storage conditions. The applicant proposes to use this program to update an effective shelf-life and minimum expiration date for the frozen HPC, Cord Blood (b) (4). The protocol assesses the stability of the (b) (4) manufacturing method (b) (4) processing) that has been used since establishment of the MD Anderson Cord Bank. The results will be used to (b) (4) shelf-life (b) (4) of HPC, Cord Blood.

Description of Stability Protocol

At the start of the study, a total of (b) (4)

Pre-specified Criteria

The acceptance criteria used in the stability studies are shown in the Table 24 below.

Table 24: Pre-Specified Criteria for Stability Study

(b) (4)

Execution of Protocol

The report of the initial stability testing executed in 2016 is contained in document S 002.022.001: *Summary Report: Stability Program*. This report summarizes the stability testing results in support of the current storage conditions. (b) (4) HPC, Cord Blood units (b) (4) from each year group) for the (b) (4) year groups (b) (4) were thawed and washed by the (b) (4) wash procedure. The tests performed are as listed in the pre-specified criteria table above.

Results Summary

Tables 25, 26, and 27 contain summaries for all the test results.

(b) (4)

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(b) (4)

Data Evaluation and Conclusion

The stability test results obtained in (b) (4) were summarized and analyzed by the applicant; there has not been any loss of stability in any of the HPC, Cord Blood units analyzed. For the (b) (4) manufacturing method under consideration for licensure, the stability data supports an expiration of (b) (4) .

Reviewer comment: *The stability data presented are acceptable. The data supports a (b) (4) expiration for the HPC, Cord Blood units manufactured by the (b) (4) methodology.*

Note: *the above (b) (4) data initially were reported as (b) (4) only. A request for the numerical (b) (4) counts was made in a December 19, 2017 information request; the numerical counts were thus submitted which were satisfactory.*

Proposed Ongoing Stability Studies

In response to December 14, 2017 request for information, the applicant proposed a plan to evaluate ongoing product stability (amendment 6 to the BLA); this plan will be executed (b) (4) . At the

(b) (4)

Table 28: Acceptance Criteria for On-going Stability Studies

(b) (4)

Reviewer comment: The plan to (b) (4) evaluate manufacturing and performance of reagents is adequate.

RETENTION SAMPLES

Table 29 below lists samples and amounts retained and temperature stored.

Table 29: Retention Sample Plan

(b) (4)

(b) (4)

Reviewer comment: *the sample retention plan is adequate.*

LOT RELEASE TESTING

This section describes the safety, purity and potency testing performed on the HPC, Cord Blood prior to release into inventory for search and distribution. In-process criteria that should be met in order for the cord blood unit to advance to the next step in manufacturing are also described in this section. These in-process criteria are not required by the Agency; however, the applicant has established these quality measures as part of quality control.

See section under 'General Information' in this memorandum for a list of third party contract testing laboratories used by the applicant.

IN-PROCESS ACCEPTANCE CRITERIA FOR PROCESSING

The collected cord blood has to meet certain pre-specified criteria to be processed (Table 30). After processing, the HPC, Cord Blood has to meet another set of criteria in order to be cryopreserved and frozen stored (Table 31).

Table 30: In-Process Acceptance Criteria for Cord Blood to be Processed

(b) (4)

Table 31: Post-Processing Criteria for Banking/Cryopreserving HPC, Cord Blood

(b) (4)

SAFETY TESTING

1. CORD BLOOD DONOR 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 HPC, Cord Blood unit. The results must be negative for all infectious disease markers, except for CMV antibody test, which is reported.

2. HEMOGLOBIN TESTING

Hemoglobinopathy is a group of disorders passed down through families (inherited) in which there is abnormal production or structure of the hemoglobin molecule. Such disorders include hemoglobin C disease, hemoglobin S-C disease, sickle cell anemia, and various types of thalassemia.

Hemoglobin is tested for homozygous hemoglobinopathies. There are two cases in which hemoglobinopathy testing is requested:

-All CBU collected must have a signed release for newborn screening results from donor mother. If a signed release was not obtained, hemoglobinopathy testing must be completed since results must be reported to NMDP.

-If an F, A Bart's (Alpha or Beta Thalassemia Disorders) result is reported on a newborn screening, then additional molecular testing is requested to determine which of the thalassemia disorders is present in newborn (CBB S 008.007.002).

Cord Blood Units are not acceptable for distribution if they contain evidence of homozygous variants hemoglobin or multiple heterozygous hemoglobin abnormal variants. In order to make this

determination hemoglobin in the red cells of each cord blood unit undergoes testing. Results are reviewed by the medical director to assure that only normal or single heterozygous hemoglobin combinations are released into inventory.

Hemoglobin testing is performed by (b) (4)

Table 32: Hemoglobinopathy

(b) (4)

Validation of Hemoglobin Testing

All three labs are qualified on basis of existence of a quality control program, Observance of GMP, test result problem/recall notification, customer complaint handling system, CAP and CLIA certification.

Reviewer Comment: Hemoglobin testing was found to be satisfactory as all three testing facilities are CAP and CLIA certified.

3. STERILITY TESTING

Sterility Test Procedure and Acceptance Criteria

The MD Anderson Cord Blood Bank has proposed to perform the Sterility Tests (for lot acceptance or release) for their HPC, Cord Blood products using the following instrument, media and conditions:

1. Incubation and Detection Instrument: A sterility test method based on the (b) (4) serviced (b) (4) and validated for bacterial and fungi testing at the MD Anderson Cancer Center. -
Reference: original submission CBB V013.o41, CBB S011.036.003.

2. Culture Media: (b) (4) designed for use in the (b) (4) Series Systems. - Reference: original submission CBB S 011.036.003.
3. Incubation temperature: (b) (4) with verified internal temperature probe. - Reference: original submission CBB V013.041, CBB S011.036.003.
4. Incubation time: (b) (4) for a negative (no growth) (b) (4) to be determined as "negative". - Reference: original submission.
5. Test Sample for the sterility assay (b) (4)
 – Reference: original submission CBB S011.036.003.
6. Acceptance Criteria for Lot-Release: Post-processing RBC by-product (from the respective HPC, Cord Blood Lot) bacterial and fungal cultures (aerobic and anaerobic) must be negative after (b) (4)
 – Reference: original submission CBB V013.086.002.

The MD Anderson Cord Blood Bank has submitted information on the working principle of sterility test using the (b) (4)

(b) (4) Aerobic/F and Anaerobic/F culture vials designed for use in the (b) (4). The applicant has also presented methods for sample processing, culture bottle inoculation, incubation and result interpretation.

Reviewer Comments:

1. The (b) (4) has been used as an (b) (4) microbial detection system in clinics and hospitals. The instrument platform and the Aerobic/F and Anaerobic/F blood culture medium in bottles are cleared by FDA (510(k) Number (b) (4)). - complies with 21 CFR § 610.12 (e)(1).
2. The Applicant has established and will follow SOPs for the sterility testing of microorganism growth in the culture-based system. The information of culture medium in standard (b) (4) is described in the (b) (4) manufacturer's product package. - complies with 21 CFR § 610.12 (c)(1)(i)(A) and 21 CFR § 610.12 (c)(1)(i)(C).
3. The sponsor has agreed any HPC, Cord Blood unit that exhibits positive evidence of microbial growth, either aerobic or anaerobic, will be deferred and discarded. Each bottle tests positive will be sent out to a qualified reference laboratory for identification of the microbial contaminant(s). The records of test samples and microbial culture identifications and characterizations should be maintained for further review.
4. Regular preventive maintenance is performed on the (b) (4) system by the manufacturer, and temperature verification is recorded (b) (4) by the Processing Facility staff – this is acceptable.

Sample used for the sterility test

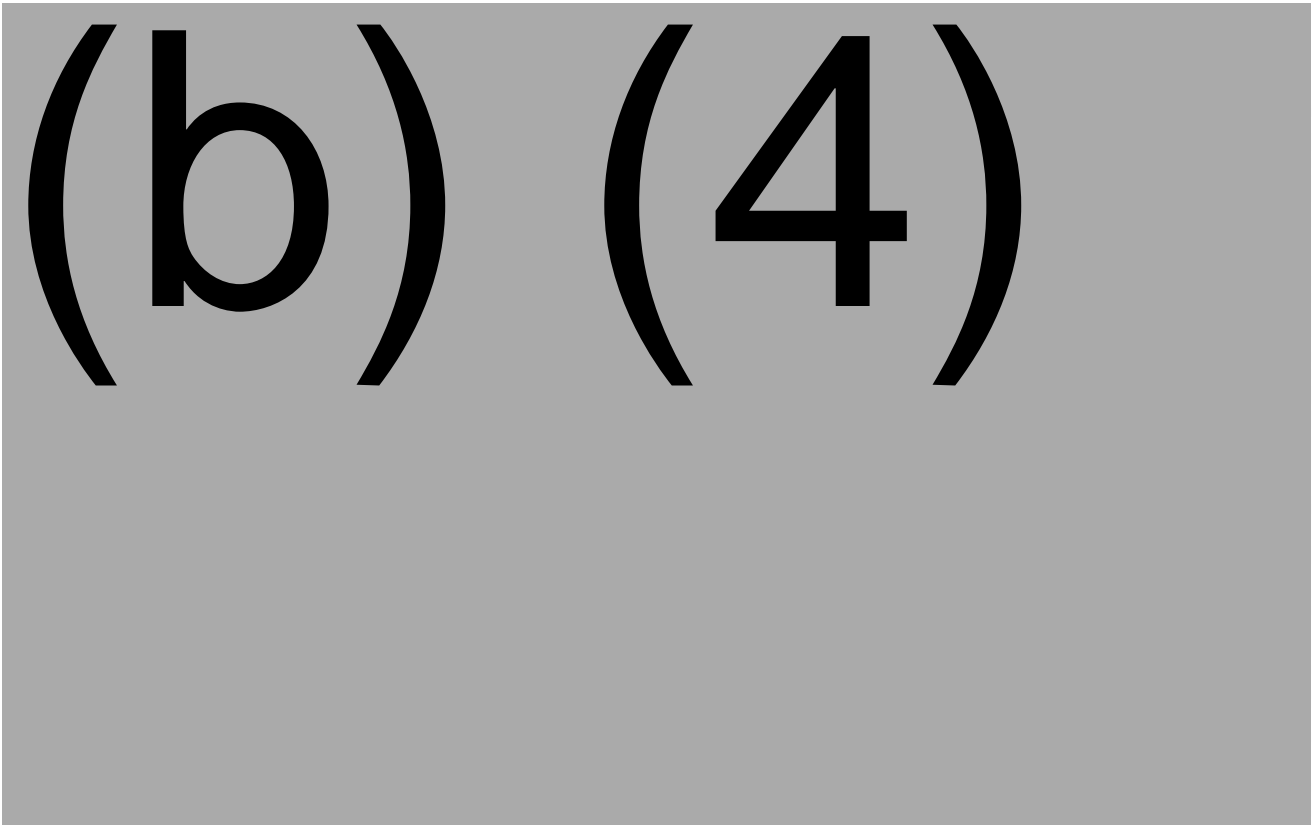

Cord blood units meeting all the pre-processing specifications are retrieved from the pass through by laboratory staff located in the manufacturing room to prepare for processing (S 007.008.005). Addition of (b) (4) of the cord blood unit volume, is required for cord blood unit processing. The MD Anderson Cord Blood Bank has proposed of testing (b) (4) RBC of post-process (b) (4)

(b) (4) (from the respective HPC, Cord Blood Lot) inoculated into each (b) (4) Aerobic/F and Anaerobic/F culture vials. The applicant is proposing this alternate sample as the final HPC, Cord Blood product volume is very small and all of it will be needed for a successful transplant in the recipient.

Reviewer Comment: *The proposed test sample of (b) (4) RBC post-processing (b) (4) of cord blood is an appropriate alternative to be used for the Sterility Test of HPC, Cord Blood manufactured by the MD Anderson Cord Blood Bank. This is based on the following: 1) closed nature of the processing method used, 2) total volume of the by-product RBC and plasma fractions (b) (4) 3) same time of origin for product and (b) (4), and 4) results of the method suitability (bacteriostasis/fungistasis) study (described below in the review)*

Sterility Test Method Validation

The validation plan was executed by (b) (4)



(b) (4)

Reviewer Comments:

1. *In the validation study, the test microorganism panel used by the applicant includes* (b) (4)

– the used panel of microorganism is broad and adequate.

2. *Growth promotion test was conducted by* (b) (4)

is an acceptable validation.

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

Test Method Suitability Study

The suitability studies for the sterility test method were conducted by the applicant using:

- (b) (4)

The summarized Detection and TTD Data for each of the testing microbes were presented in the submitted method suitability study.

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4. (b) (4)

Note: (b) (4)

Results- Test Method Suitability Study

1. "All QC procedures for equipment and reagents used in this study are performed in accordance with the submitted protocols"
2. Growth of organism is detected in aerobic and/or anaerobic bottles as expected for the (b) (4) different tested microorganisms as the positive controls.
3. Post-processing RBC (b) (4) (from the respective HPC, Cord Blood Lot) (b) (4) must be negative after (b) (4) of cultivation.

Reviewer Comments:

1. As all microorganisms (including the (b) (4)) grew in the presence of the test sample (b) (4) and less than (b) (4) we conclude that the proposed (b) (4) test sample does not have a significant bacteriostatic/fungistatic effect on any of the microorganisms tested.
2. Based on the data of validation study and suitability study, we agree that the negative sterility testing results of proposed sterility methodology using th (b) (4) are acceptable criteria for release of the HPC cord blood products.

Note: In addition, the study showed that the TTD of a (b) (4)

. As commented above, the (b) (4) appeared

to be more sensitive to unspecified bacteriostatic factors such as residual antibiotics that were present in (b) (4) cord blood. We agree that the proposed test sample of (b) (4) acceptable. But, this does not mean the (b) (4) are acceptable in the validation study. Since more than 98% of bacteria are considered un-cultivable using our current microbial culture systems, not all strains/isolates of (b) (4) or any species of bacteria isolated locally from different environmental sources or clinical settings will grow in the testing matrix with TTD less than (b) (4), using (b) (4) microbial culture system. However, we do expect all the established testing species of microbes known to be able to grow in the aerobic and/or anaerobic microbial culture systems will grow with TTD less than (b) (4), when inoculated with the specified concentration in the validation study.

Reviewer Comments on Other Issues:

1. The common use of intrapartum antibiotics raises the question about the potential presence for residual antibiotics in the cord blood product. The bactericidal and/or bacteriostatic effects of antibiotics may affect the sterility test sensitivity and results of the processed cord blood products.
2. The (b) (4) using Aerobic/F and Anaerobic/F culture vials with culture broth containing resins to remove antibiotics and some other possible inhibitors that could interfere microbial growth in the blood samples. There are studies that support (b) (4) using Aerobic/F and Anaerobic/F culture vials has higher culture sensitivity in recovering microbes in blood samples containing residual antibiotics. However, it is difficult to assess the true advantage of using the (b) (4) for sterility test of cord blood products.


Conclusion and Recommendations

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

IDENTITY TESTING

1. HUMAN LEUKOCYTE ANTIGEN (HLA) TYPING

(b) (4)

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(b) (4)


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Table 35: HLA-Typing Assay

(b) (4)

(b) (4)

Validation of HLA Typing

Labs at The University of Texas MD Anderson Cancer Center (b) (4) have CLIA certification, CAP accreditation and ASHI certification. All HLA typing results received by NMDP pass through a rigorous override process which will flag any discrepant results for further review by NMDP staff. In addition, information provided during internal quality testing data reveals that a unit is unsuitable for transplantation, the unit is removed from the registry and the NMDP is notified.

Reviewer Comment: HLA testing is adequate as the HLA typing labs are CLIA certified along with accreditation from CAP and ASHI. Also, the SOPs are in place to ensure that the test results are correctly linked to the individual donors. Initially the firm had not provided the CLIA certificate for (b) (4). This the certificate was submitted to FDA as an amendment 3.

2. ABO/Rh BLOOD GROUP TYPING

(b) (4)

Table 36: Identity

(b) (4)

Reviewer Comment: The blood group testing was found to be adequate as all test systems and reagents are under CLIA high complexity testing designations.

PURITY AND POTENCY

1. TOTAL NUCLEATED CELL COUNT

Total Nucleated Count is done on the (b) (4) which is located at MD Anderson Cord Blood Center testing lab. The system is used to generate a report of (b) (4)

[REDACTED]

The table below gives the overview of the TNC timings:

Table 37: Sample Preparation for Total Nucleated Cell Count

(b) (4)

Results are reviewed by the operator and report is supplied to the Cord Blood laboratory. Nucleated red blood cells (nRBC) are included in the complete blood count (CBC) under "NRBC". Cord blood units with a NRBC (Nucleated red blood cell) count greater than (b) (4) of Nucleated cells/ml X 10⁶ count will be discarded.

CBC results are received by the Cord Blood laboratory and used with the following formula to calculate TNC:

TNC= (b) (4)

Validation of Total Nucleated Count (b) (4)

Instrument Qualification:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

TNC Count Validation:

The sponsor has submitted qualifying data to support the process validation. The process validation was done by (b) (4)

(b) (4)

Reviewer Comment: (b) (4) TNC qualification and validation was found to be adequate. TNC is performed on FDA approved instrument. The instrument is (b) (4) evaluated for the proper functioning along with (b) (4) maintenance performed by the technologist recommended by (b) (4) operator's manual. Calibration is performed during installation and verified every (b) (4) during scheduled preventative maintenance (PM) by a (b) (4) service representative. In addition, sponsor has (b) (4) instrument that will perform the TNC.

2. VIABILITY, CD34 (b) (4) COUNTS: FLOW CYTOMETRY BASED ASSAYS

(b) (4)

(b) (4)

(b) (4)

[Redacted text block]

Description of Protocol

(b) (4)

[Redacted text block]

Reviewer comment: During the telecon that was held on October 11, we recommended that the Applicant updates their SOP to indicate that the holding time after lyse and before sample acquisition should not exceed (b) (4) as recommended in the CD34 (b) (4) package insert. The sponsor provided the updated CBB S 012.012.005 in amendments #7 (submission 125657.008) on May 14, 2018 indicating that they will acquire the sample within (b) (4) of the end of lysing. This is acceptable

Pre-Specified Acceptance Criteria

To consider a Cord Blood Unit suitable for release, the processed unit must contain $\geq 1.25 \times 10^6$ viable CD34+ cells.

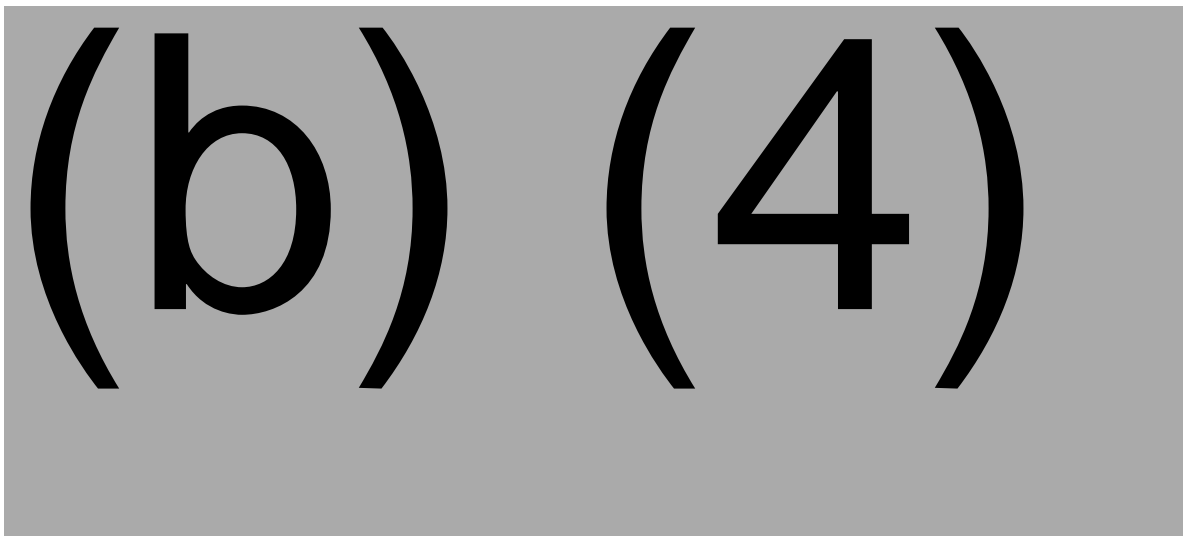
Sample: HPC, Cord Blood final product

Results

Data are acquired and analyzed on (b) (4) clinical software per CBB S 012.012 using the following (b) (4) template

Figure 6 below shows the flow cytometry (b) (4) template and representative data analysis.

Figure 6: Flow Cytometry (b) (4) Template for Data Analysis



Flow Cytometry Assay Validation Summary

Summary of the validation studies is presented in V 013.096, and 3.2.P.5.3. Validation of Analytical Procedures

Test Kit Reagent Qualification

The sponsor uses (b) (4)) for CD 34 + cells enumeration. This kit is cleared for use with fresh and post-thaw cord blood specimens. The assay is designed to enumerate CD34 cells using a (b) (4)

(b) (4)

Qualification of New Reagent Lot

- Each new lot and each new shipment received of (b) (4) controls and reagents used for flow cytometry are qualified prior to use per CBB S 012.013 (b) (4) Cytometer: Preparation of Reagents and Samples and Reagent Qualification”
- Qualification of new lots and new shipments of reagents and control qualification are documented on CBB W 081.228 (b) (4) Reagent Qualification.”
- The completed CBB W 081.228 worksheet will be reviewed and released for use by Quality Unit when assayed control values are within expected range before use on clinical samples.

Flow Cytometer Instrument

(b) (4)

Note: In response to agency request for additional information on October 11, 2017, the Applicant indicated that currently they have a (b) (4) flow cytometer in place (b) (4) to measure CD34 absolute count. All provided validation studies were performed on this cytometer. We asked the sponsor to provide an action plan during the period of instrument breakdown. The Applicant states that in future they are planning to use flow cytometer (b) (4). On a telecon that was held on February 9, 2018, we clarified to the Applicant that assessing product potency, (b) (4) is critical for the release of Cord Blood Unit. As such, currently, they cannot license any cord blood unit during the period of instrument breakdown until they will fully validate the (b) (4) cytometer and provide an acceptable CD34 comparability results between (b) (4) cytometers. The Applicant agreed and states that the current plan is to license the cord Blood using (b) (4) flow cytometer (b) (4) and will provide additional studies in a supplement to this BLA after licensure before using (b) (4).

Quality Controls

- (b) (4)

Equipment Validation Requirements

- Installation Qualification: installation per the manufacturer's specifications. Testing is completed by a (b) (4). The Applicant provided a certificate of Calibration.
- Operational Qualification: verification of functionality per manufacturer's operational specification before actual use. Testing is completed by a (b) (4).
- Performance Qualification: demonstration that equipment performs as expected for its intended use and meets performance specifications established by the manufacturer.

Note: The Applicant uses a (b) (4) flow cytometer (b) (4) for the flow cytometric analysis on cord blood units. The firm provided (b) (4) System Installation Qualification, Certificate of Calibration and employee training records as requested. This is acceptable.

Method Validation

(b) (4)

The Applicant provided data on accuracy, precision (repeatability and intermediate precision), and linearity on both Clinical Software, CBB V 013.096, and Research Software, CBB V: 013.098 using control materials with designated CD34+ concentrations as well as cord blood units. The provided validation studies are summarized in the tables below.

Note: (b) (4) was cleared to be used to enumerate CD34 absolute count on clinical software using fresh and thawed cord blood specimens. During the inspection in February 26, the Applicant indicated that they are using (b) (4) on clinical software to enumerate CD34 for product release (Fresh cord blood units) and (b) (4) on the research software for collecting data for product stability (Cryopreserved

cord blood units). We advised the Applicant to use the clinical software with (b) (4) to generate both the product release and the stability data. The sponsor agreed using only one platform (clinical software) for both fresh and cryopreserved cord blood units as recommended. In addition, the Applicant provided data to demonstrate comparability between the clinical software and research software in (CBBV: 013.104). The provided test results for the comparability study met the predefined acceptance criteria (b) (4) .

Accuracy

Method: (b) (4)

[REDACTED]

Precision

- (b) (4)

[REDACTED]

Linearity

The linearity of an analytical procedure is the ability of the assay to obtain test results which are directly proportional to the concentrations of analyte in the sample within a given range.

Test Methodology- Control Material

(b) (4)

[REDACTED]

Test Methodology- Cord Blood Unit

(b) (4)

[Redacted text block containing approximately 10 lines of information]

Note: In the original submission, the Applicant failed to demonstrate (b) (4) linearity on the clinical software. We worked closely with the Applicant to solve this issue. The Applicant followed our recommendations and succeeded to demonstrate (b) (4) linearity and submitted an addendum (CBB VA1:013.096.001 which includes the requested information. The Applicant provided sufficient information with supporting documents to demonstrate (b) (4) linearity.

Table 38: Results of CD34 Validation Study on (b) (4) Clinical Software

(b) (4)

(b) (4)

Note: Note (b) (4) lots were not available from the manufacturer. Testing was completed utilizing (b) (4) that were shipped to the CBB on different dates (ship dates 03-07-2017 and 03-30-2017). This is acceptable.

CD34 Validation Study on (b) (4) Research Software

In addition, the Applicant performed the following validation testing using frozen/thawed samples

(b) (4) research software

Table 39: Pre-Specified Criteria for Validation

(b) (4)

(b) (4)

Summary: Comparison of Clinical and Research Platform CD34+(b) (4) Analysis Methodologies for Washed Cord Blood Unit Samples (CBB V:013.104)

The Applicant provided the following study to demonstrate comparability between CD34+(b) (4) data obtained from (b) (4) Clinical software and from the laboratory prepared (b) (4)

Research software. (b) (4)

The Applicant provided acceptable comparability data between both methodologies in CBBV: 013.104.

Note: The Applicant has provided sufficient information about the flow cytometry assay used to measure CD34 cells, and adequately validated the flow cytometry 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 flow cytometry laboratory has provided adequate information about procedures for instrument quality control, instrument validation, and training of staff.

3. COLONY FORMING CELLS (CFU) ASSAY

(b) (4)

[Redacted text block]

Method

The CFU assay is performed in Cord Blood Testing Laboratory of the MD Anderson Cord Blood Center using (b) (4)

[Redacted text block]

Results: The results of the colony forming unit assay must demonstrate growth (CBB S 006.003.002).

Validation of CFU assay

Validation for the Colony Forming Unit (CFU) Assay was performed to provide documented evidence that the assay demonstrates (b) (4)

Three studies were performed to see if:

1. CFU assay produces expected results (growth observed). (b) (4)
- [Redacted text block]

(b) (4)

The validation plan and protocol was executed by trained CBB Personnel trained to this protocol and CBB S006.003 Colony Forming Unit (CFU) Assay: Set-up, enumeration and reporting. CBB Manufacturing personnel processed samples per the procedures in which they are trained. Quality Assurance (QA) is responsible for reviewing and approving the summary report, and for ensuring compliance of this validation with applicable MD Anderson Cord Blood bank procedures, policies and regulatory agencies. Additionally, each lot and each shipment is qualified (CBB S 006.011) at the CBB prior to use.

Reviewer Comment: CFU assay was found to be sufficiently validated. The results from (b) (4) samples were tested for (b) (4) performed by (b) (4) technologists were compared and the data was found to be within (b) (4). The total of (b) (4) samples (b) (4) which showed growth, which is acceptable. There are multiple steps enforced where the CFU data is reviewed, before the product is released to the registry. In addition, only the CBUs that demonstrate the growth are approved for banking.

RELEASE OF HPC, CORD BLOOD FOR REGISTRY LISTING AND DISTRIBUTION

Each lot of HPC, Cord Blood is maintained in the (b) (4) freezer under quarantine until all results for donor eligibility determination, lot release testing, and cryopreservation criteria are reviewed and acceptable for banking by the Quality Unit. These units meeting all acceptance criteria will be released in to the National Marrow Donor Program (NMDP) searchable web-based data base, CordSource system, an online transactional search tool. HPC, Cord Blood product data can be accesses by registered transplant center coordinators, treating physicians, and transplant center medical directors.

Transplant centers or registries make a search request for a HPC, Cord Blood through CordSource. At the time of request, an NMDP application-generated email notification is sent to the cord bank. A hold is place on the HPC, Cord Blood unit and a confirmatory HLA-typing is requested and scheduled; a (b) (4) and shipped to NMDP designated third party lab for HLA typing. A comprehensive review of file documentation is also performed by the Medical Director and

then by the Quality Unit. After, the HLA typing results are confirmed, the HPC, Cord Blood unit is prepared for shipment/distribution to the transplant center.

Table 40: HPC, Cord Blood Criteria for Release for Registry Listing

Product Characteristics	Testing	Specification
Safety	Infectious Diseases Testing Required (21 CFR 1271.45 through 1271.90) HBsAg Anti-Hep B core Anti-HCV Anti-HIV-1/2 Anti-HTLV-1/2 Anti-Trypanosoma cruzi (Chagas) HIV RNA/HCV RNA/HBV DNA West Nile Virus RNA Syphilis Cytomegalovirus (CMV)	All tests negative, except CMV CMV results-Report
	Sterility	(b) (4)
	Hemoglobinopathy	(b) (4)
Purity and Potency	Total CD34+ cell count	$\geq 1.25 \times 10^6$ /HPC, Cord Blood
	Total Nucleated Cell (TNC) count (per HPC, Cord Blood)	(b) (4)
	Viability Nucleated cell (b) (4)	(b) (4)
	Viability- CD34+ cells (b) (4)	(b) (4)
	Colony Forming Units (CFU) assay	Growth
Identity	Initial Human Leukocyte Antigen (HLA)	Report

	Confirmatory HLA	Report
	ABO/Rh Type	Report

REAGENTS USED IN MANUFACTURING

Citrate Phosphate Dextrose (CPD)

Citrate Phosphate Dextrose is an (b) (4) under FDA approved (b) (4) .

(b) (4)

DMSO/Dextran 40

The cryoprotectant used in manufacture is a mixture DMSO and Dextran 40 (b) (4) v DMSO and (b) (4) Dextran 40 (b) (4)

CONTAINER CLOSURES

All containers and closures that are in direct contact with the HPC, Cord Blood are sterile and FDA approved devices.

Collection Bag

Cord blood is collected into specifically designed sterile collection bags from (b) (4) . The collection bag is FDA approved under (b) (4)

(b) (4)

Processing Kit

The sterile single-use processing kit (b) (4) is manufactured and sold by Biosafe under 510k (b) (4). The processing set was specifically made for use on the FDA 510k cleared (b) (4) device. Each pre-assembled processing kit comes individually packaged in a sealed (b) (4)

Cryobag (Freezing Bag): The HPC, Cord Blood product (the final product) is packaged in the Biosafe (b) (4) cryobag, (b) (4) cryobag. The cryobag is comprised of two compartments, an 80% and 20% compartments. The cryobag is the primary container for the HPC Cord Blood (buffy coat or leuko-rich fraction) product and is provided as an integrally attached part of the (b) (4) .4b sterile single use processing kit manufactured and sold by Biosafe under 510k (b) (4).

Overwrap

The (b) (4) overwrap is designed to enclose the cryobag containing the HPC, Cord Blood unit. The overwrap functions as secondary container closure during cryopreservation and storage up to the point of release for distribution. The overwrap is manufactured by (b) (4)

Stainless Steel Canister

The stainless steel canister acts as secondary packaging, enclosing the cryobag it its overwrap.

CONTROL OF ASEPTIC MANIPULATIONS

MD Anderson Cord bank has implemented a multi-level approach to prevent contamination and cross-contamination of in the manufacture of the HPC, Cord Blood. All manufacturing activity for the production of HPC, Cord Blood is performed in an (b) (4) classified clean room processing facility. All product manipulation is performed using a functionally closed system comprising of sterile, disposable, single-use materials for manufacturing. The addition of excipients and removal of samples are performed using sterile connection devices which allows for all manipulations to be performed in the (b) (4) environment. Function of the closed system has been confirmed through the execution of a media fills as well as through the maintenance of product sterility as reported in the process validation. All equipment used in manufacture of HPC, Cord Blood is cleaned before and after use for each unit

processed, using a (b) (4) followed by (b) (4). A differential pressure cascade is established between the (b) (4) and adjacent (b) (4) rooms within the facility. Defined patterns of flow are established for personnel, supplies, and pre-manufacturing cord blood units entering the facility as well as post-manufacturing HPC, Cord Blood and waste exiting the facility. In addition, all staff working in the clean room are required to gown prior to entering the classified laboratory space.

LABELING AND TRACKING

A unique cord blood identification number (CBID) is assigned for each donation and maintained throughout the collection, transport, processing, cryopreservation, storage and distribution. During accessioning, the barcoded CBID assigned/affixed to the unit during collection is scanned into the (b) (4) (cord blood information system) computer system; the collection date and time on the label are also input in the (b) (4). Thereafter, all subsequent labeling is generated by scanning the CBID affixed on the collection bag.

The applicant uses ISBT 128 labeling and seeks exemption from the NDC code.

Donor Tracking and Labeling

See Donor Eligibility and Collections sections of this review for Donor tracking and labeling.

Partial and Package Labels

A partial label is affixed to the HPC, Cord Blood two-compartment container during processing and cryopreservation. At the time of shipping and distribution, the full package label is attached to the canister with a tie-tag. This is because at the time of cryopreservation, not all release test results will be available to determine if the HPC, Cord Blood meets the criteria for licensure. The tie-tag label will contain the product expiration and license number. Figure 8 shows the full label that is attached to the HPC, Cord Blood at the time of shipping for distribution. This label is applied to a tie-tag which is in turn attached to the steel canister containing the product (shown in Figures 9 and 10).

Figure 7: HPC, Cord Blood Container Partial Label

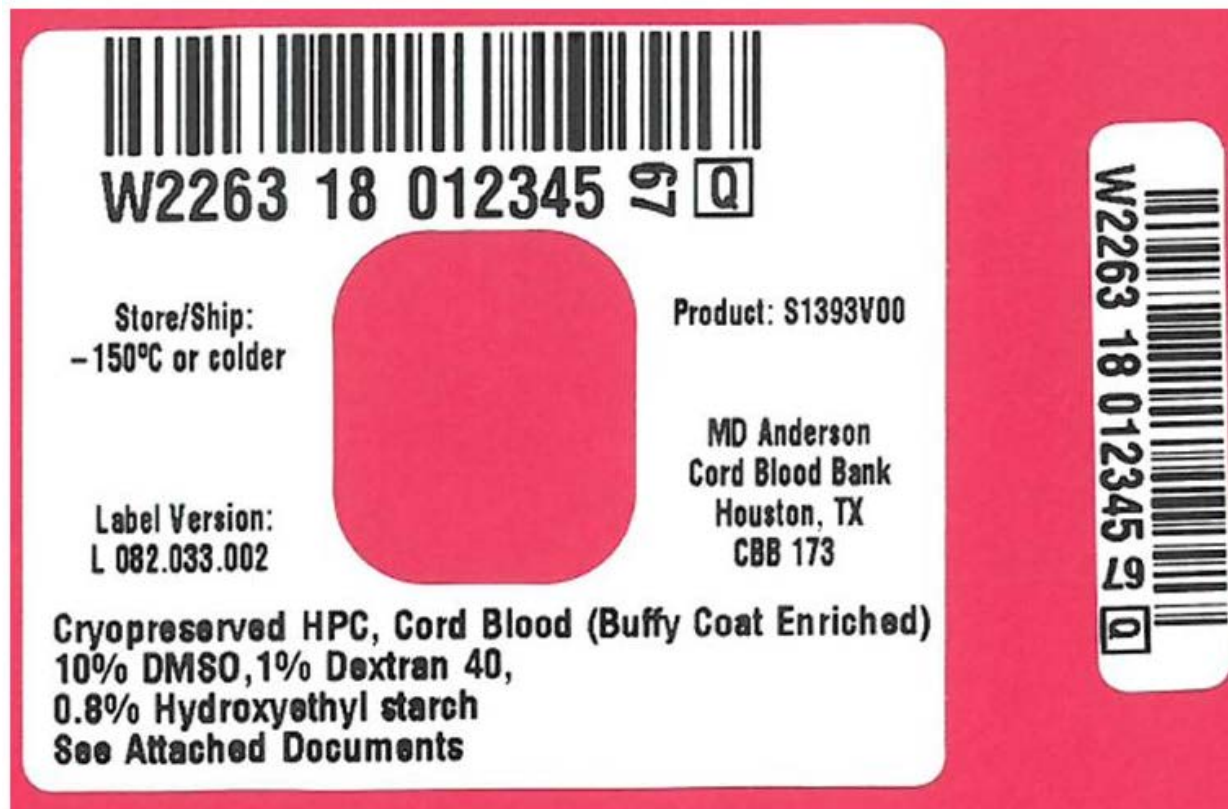


Figure 8: HPC, Cord Blood Package Label

 W2263 18 012345  R Collection Date  0171720808 21 JUN 2017 08:08 Properly Identify Intended Recipient and Product Rx only	 B Rh POSITIVE 7300 FOR USE BY INTENDED RECIPIENT ONLY INTENDED RECIPIENT Name: Doe, John DOB: 12/25/1992 ID: 123-456-7 DO NOT IRRADIATE DO NOT USE LEUKOREDUCTION FILTER
 S1393V00 CRYOPRESERVED HPC, CORD BLOOD Buffy Coat Enriched Approx. 25 mL 10% DMSO, 1% DEXTRAN 40, 0.8% Hydroxyethyl starch Store at -150°C or colder See package insert for full prescribing information and instructions for preparation	 Expiration Date 0221720808 21 JUN 2022 08:08 ADDITIONAL CBU IDENTIFIERS NMDP ID: 9876-5432-1 Local ID: 012345 Collected and Processed By MD Anderson Cord Blood Bank 1841 Old Spanish Trail, Houston, TX US License: XXXX Label Version: L 082.027.002

Figure 9: Package Label Attached to Tie-Tag (Folded over two sides of Tie-Tag)



COMPUTER SYSTEMS

There are three computer systems in operation; two are on used in facility operations and the third is for listing on the NMDP registry.

(b) (4) the Cord Blood Bank (CBB) data base. The (b) (4) application is used for the collection of data including collection, manufacturing, and shipment data. It serves as the source for the generation of the unique cord blood identifier (CBID) that is assigned to each cord blood unit collected. The CBID is a unique, incrementing integer that serves as the key value in the system. At the time of CBID generation, batches of labels are generated; these are used for all consent and collection activities.

All maternal demographic, maternal risk, and family health history information recorded during donor screening is captured on an electronic work sheet (b) (4) that is imported into (b) (4) application. All maternal and cord testing data, including infectious disease and ABO/Rh testing results are imported into the system electronically from the vendor. Hemoglobinopathy and sterility test results are entered manually.

Cord blood unit processing data from collection to cryopreservation is captured in (b) (4). All labeling generated during processing is reviewed and scanned back into the application to ensure they are - correct. The consumables and equipment utilized at each step of the process are recorded into the (b) (4) system.

(b) (4) : is an inventory management application that is used to manage supplies and equipment. Inventory received is accessioned and barcoded for traceability. The (b) (4) component is integrated into the (b) (4) application and is used to track supplies and equipment during product manufacturing.

(b) (4) : Cord Blood Bank application to assist users in documenting and approving their daily work functions, it is interfaced with (b) (4) system. The (b) (4) workflow application is used to track all tasks from collection through listing in search inventory. Data flagged for review prompts a designated staff to review and evaluate in order to complete the task. All decisions regarding conformance/non-conformance are made by trained and qualified staff and recorded in the system. The outcome of Donor eligibility determination is recorded in in (b) (4) and confirmed by the Medical director in this system.

(b) (4) operated by the National Marrow Donor Program (NMDP) for management of the National Cord Blood Registry; the application is developed and hosted by the NMDP. The primary function of (b) (4) is the listing and management of cord blood units within the NMDP registry. It is also used to manage HPC, Cord Blood request received from NMDP.

ENVIRONMENTAL ASSESSMENT

The applicant requests a categorical exclusion from the preparation of an environmental impact statement based on 21 CFR 25.31(c). The manufacturing process does not alter significantly the concentration or distribution of the substance, its metabolites or degradation products in the environment.

EMERGENCY PRODUCT RECOVERY (SOP S 007.024.001)

Instructions for emergency product recovery in the event of primary container failure, is part of the prescribing information, in the “Instructions for Preparation for Infusion” section. Because of the fragility of cryopreservation bags at liquid nitrogen temperatures ($\geq -150^{\circ}\text{C}$), bag breakage may occur on occasion, potentially resulting in the leakage and contamination of the product. The product may need to be recovered if additional cell resources are not available. The applicant describes how cells may be salvaged if container breakage occurs.

Prior to start of the thawing process, the cryobag is examined for integrity. The product is then transferred into a Ziplock bag before placing in the water bath.

After thaw if the bag is compromised, immediately transfer the Ziplock bag containing the cells to the biosafety cabinet. Notify the transplant physician as soon as possible about the situation and possible product contamination.

Using aseptic technique, slowly remove the cryobag from the Ziplock bag and isolate the breakage area with a hemostat.

Then place the product bag back in the Ziplock bag.

Aseptically insert a sampling site coupler into the available ports on the cryobag and transfer the product into an appropriate sized transfer pack.

Attach a needle to a 60 ml syringe and use it to remove the contents of the cryobag.

Record the volume of the product in the syringe and empty the contents of the syringe into an appropriate size transfer pack.

Attach a long blunt needle to a 60 ml syringe and use it to aspirate any product that may have spilled into the sterile Ziplock bag. Record the volume of the spill.

If the volume is minimal, consider excluding from the product.

Transfer the collected contents to transfer pack using a syringe, if a decision is made to include the spill for the Ziplock bag. Take a sample for cell count using a syringe.

Complete wash of the product. Take pictures of the bag and include in the incident report.

Perform sterility testing on the washed product.

The Transplant Center is instructed to contact the MD Anderson Cord Blood Bank at 1-713-563-8000 or 713-794-1908 if during thawing, any portion of the product container appears to be damaged or compromised. Save the ruptured cryobag if possible. The Cord Blood Bank will provide further instructions for return of the container, if required for investigation.

Reviewer comment: *The applicant's procedures to recover the product in case of container failure is adequate.*

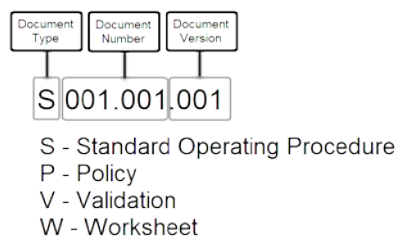
Figure 10: Package Label Attached to Steel Canister containing HPC, Cord Blood



Document labeling

Document numbering system used by applicant for SOPs, Worksheets, Policy, and Validation documents, follows the following format in the Figure 11 below.

Figure 11: Document Labeling



The document version number is typically removed for inter-document references to other controlled documents which typically only use the Document Type and Document Number as the reference.