Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: **125407/0** Hematopoietic Progenitor Cells, Cord (HPC-C)

Duke University School of Medicine (License No. 1870)

From: Nancy Waites, Facility Reviewer, OCBQ/DMPQ/HFM-675

Through: Carolyn Renshaw, Branch Chief /OCBQ/DMPQ/MRB1/HFM-675

Cc: Mark Davidson, RPM, OCTGT/RMS / HFM-700
Denise Gavin, PhD, Chair, OCTGT/DCGT/GTB /HFM-720

Subject: Review of BLA submitted by Duke University School of Medicine, received 09 Sep 2011, to obtain approval for minimally manipulated, unrelated allogeneic placental/ umbilical hematopoietic progenitor cells (HPC-C).

Recommendation: I recommend approval of this submission for the manufacture of minimally manipulated cord blood as long as the Product Office does not have any issues.

Overview

This application is for hematopoietic progenitor cells, cord (HPC-C) manufactured by the Carolinas Cord Blood Bank (CCBB) to be distributed for unrelated donor cord blood transplantation. This product will be administered by infusion, and the CCBB recommends that all products be thawed and washed before administration. The thawing and washing procedure is sent with each product to the transplant center. The dosage of each product will be decided by the transplant center.

This product is intended for hematopoietic reconstitution in patients with any of the following diseases:

- Hematological malignancies
- Certain lysosomal storage and peroxisomal enzyme deficiency disorders
    - Hurler Syndrome (MPSI)
    - Krabbe Disease (Globoid Leukodystrophy)
    - X-linked Adrenoleukodystropy
- Primary immunodeficiency Diseases
- Bone Marrow Failure
- Beta Thalassemia

The HPC Cord Blood product contains a minimum of -(b)(4)- nucleated cells in a (b)(4) mL mixture of Citrate Phosphate Dextrose, 10% DMSO, 1% Dextran, and (b)(4) Hespan. The cells have (b)(4) viability pre-cryopreservation and a minimum of 1.25 x 10^6 viable, CD34+ cells. The nucleated cell count, ----------(b)(4)----------, and CD34+ cell count for each individual product is listed in the labeling information sent with each individual unit so that per kilogram dosing of the HPC Cord Blood product can be calculated. The product is frozen and stored at -(b)(4)- in a two-compartment bag resulting in an 80/20 split. The compartments can be accessed separately, if needed. Once thawed, the product is liquid with a pink to red color.

Changes to BLA after Submission
Originally, CCBB was seeking licensure of both the ----------(b)(4)---------- processing of the cord blood units along with the ability to ----------(b)(4)-------- if the CBU did not meet in-process specifications. In addition, CCBB was seeking to license CBUs that were manufactured in both ----------(b)(4)----------. On 28 Mar 2012, CCBB amended their application to state that they were seeking licensure for only the units processed using the ---(b)(4)--- process in ---(b)(4)--- since 29 Sep 2008. In addition, CCBB modified their application to state that the -------(b)(4)------- would not be included in the licensed process.

Therefore, this review does **not** include information on the --(b)(4)-- processing of the collected cord blood units, ------(b)(4)-------, or information on ---(b)(4)---.

Review

CMC Section
HPC-C Description and Characterization
This information falls under the Product Office's responsibility for review. I did not review this section.

Manufacturer(s)

Organizational Information
The following chart lists the pertinent organizational information for each manufacturer, including those under contract, agreement, or other arrangement to perform a manufacturing step. These organizations include, but are not limited to, all collection sites that act as Duke's agent(s) and laboratory(ies) performing testing of donor samples for relevant communicable disease agents and product sterility testing.

Name	Address	FEI No. / FDA Registration No.	Function
Carolinas Cord Blood Bank	North Pavilion Building Suite 1400 2400 Pratt Street	FEI 3002663011	Manufacturing

Name	Address	FEI No. / FDA Registration No.	Function
Processing Laboratory	Durham, NC 27705 Phone:919.668.2066		
Duke University Hospital (site #21)	2100 Erwin Road Durham, NC 27705 Phone: 919.681.0374		Cord Blood Collection Site
Durham Regional Hospital (site #22)	3643 N. Roxboro Road Durham, NC 27704 Phone: 919.470.8295		Cord Blood Collection Site
Memorial Hospital at the University of North Carolina-Chapel Hill (site #23)	101 Manning Drive Chapel Hill, NC 27599 Phone: 919.843.0918		Cord Blood Collection Site
Rex Hospital (site #49)	4420 Lake Boone Trail Raleigh, NC 27607 Phone: 919.784.2276		Cord Blood Collection Site
Women's Hospital of Greensboro (site #70)	801 Green Valley Road Greensboro, NC 27408 Phone: 336.832.4836		Cord Blood Collection Site
Womack Army Medical Center (site #90)	2817 Reilly Road Ft. Bragg, NC 28310 Phone: 910.643.2517		Cord Blood Collection Site
Brigham and Women's Hospital (site #30)	75 Francis Street Boston, MA 02115 Phone: 617.632.2434		Cord Blood Collection Site
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Name	Address	FEI No. / FDA Registration No.	Function
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Robertson Clinical and Translational Cell Therapy Research Lab	North Pavilion Building Suite 9550 2400 Pratt Street Durham, NC 27705 Phone: 919.681.6615		Laboratory Performing Release Potency Testing-(b)(4) Assays

Applicant Contact Information
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Vice Chancellor for Academic Affairs
DUMC Box 2927
125 Davison Building
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Additional Contact Information:
Bruce Burnett, PhD, RAC
Director, Regulatory Affairs
Hock Plaza, 2424 Erwin Road, Suite 402
Durham, NC 27705
Phone: 919.668.7178
Fax: 919.668.7868

Manufacturing and Cryostorage Facilities Overview
The Carolinas Cord Blood Bank (CCBB) occupies approximately ----------(b)(4)---------- in the Duke University North Pavilion Building located at 2400 Pratt Street Durham, NC 27705.

The North Pavilion Building is access controlled through the security station that is at the plaza level entrance of the North Pavilion Building and is staffed 24/7. After hours (6 pm-6 am) access to the building is by key card. Access to CCBB within the North Pavilion Building is also controlled by card key readers at the entrances to CCBB. This would include access to the BioArchive storage equipment.

The processing laboratory, --(b)(4)--, is located on the (b)(4) level and is approximately -------(b)(4)------. The storage area, ----------(b)(4)----------, is located on the

(b)(4) level and is approximately --------(b)(4)------. The Potency Laboratory is located on the (b)(4) floor and consists of ----(b)(4)----. The Duke Hospital Stem Cell Laboratory (STCL), the site of some in process testing (----------(b)(4)---------- assays) is located ----(b)(4)---- from the CCBB processing laboratory. In addition, the CCBB has approximately -----(b)(4)----- of freezer space located on the -(b)(4)- floor, Room (b)(4) and Room (b)(4) of the North Pavilion Building.

The processing laboratory is dedicated space and consists of the following areas: Receiving/Filing, Data Entry / Shipping, Laboratory Operations Supervisor Office, Laboratory Manager Office, Processing / Cryopreservation/Testing, Supply, and Freezing/Storage.

The North Pavilion, Suite (b)(4) laboratory is a purpose-built, modern laboratory space designed to accept incoming CBUs and process/cryopreserve them. The facility is of suitable size, construction, and location to facilitate cleaning, maintenance, and proper operations. The flooring, walls and ceilings are composed of smooth, hard, impermeable building materials that are cleanable. The flooring is homogeneous (b)(4) with an integral coved flash cover base. The walls consist of painted -(b)(4)- wall board. The ceiling is composed of ----(b)(4)---- panels with gasketed grids. The doors and frames are (b)(4). The casework is (b)(4), and countertops are (b)(4). The Air Handling Unit is a ----------(b)(4)----------. The room is positively pressurized (b)(4) relative to adjacent spaces. There are ------(b)(4)------- per hour (recirculation) with ----(b)(4)---- per hour (ventilation).

Floor Diagrams

CCBB Processing Laboratory floor diagrams are included within the submission and they describe the layout of the facility, the division of the laboratory space, the overall manufacturing flow, and the product, personnel, equipment, and waste flows within this space.

The CCBB Processing Laboratory is broadly divided into 6 main manufacturing areas, including receiving; pre-qualification; processing; post-processing counts and sample preparation; cryoprotectant infusion; and cryopreservation, long-term storage, and shipping preparation. Additionally, there is one large area for storage of supplies that have been released from quarantine.

The following listed figures were included in the submission.

- Figure A.1.1.3-1: CCBB Processing Laboratory.
- Figure A.1.1.3-2: Overall Product and Manufacturing Flow Diagram.
- Figure A.1.1.3-3: Overall Manufacturing Flow, Steps (b)(4).
- Figure A.1.1.3-4: Overall Manufacturing Flow Steps (b)(4).
- Figure A.1.1.3-5: Personnel, Waste, and Equipment Location and Flow.

Personnel, Waste, and Equipment Flow

After entering through the main door of the facility, personnel enter the receiving area or the main processing space, which is separated from this internal corridor by another door.

Due to the station approach to processing a cord blood unit (CBU), personnel can move freely throughout the laboratory space, although per CCBB, a technician is only moving between a couple of different stations. To leave the laboratory space, personnel exit by the same path through which they entered.

There are (b)(4) main locations in the laboratory for waste disposal. Disposal could include a CBU that does not meet prequalification standards or the remaining red blood cells/plasma following processing. All waste is discarded into a biohazard container, and Duke Environmental Services is contracted for waste removal. Biohazard waste containers are removed through either of the (b)(4) main doors that allow personnel movement into and out of the laboratory.

Major equipment is located throughout the laboratory, and these locations are designated in Figure A.1.1.3-5 within the submission.

Cord Blood Unit Processing Overview
A description of the manufacturing process for any HPC-C product consists of the steps listed below. The steps that are in **bold** type are included in this review since they fall under DMPQ review responsibilities. The steps not in **bold** type are the sole responsibility of the Product Office to review and are not included in this review.

- Donor Recruitment and Consent
- Donor Screening
- **Cord Blood Collection**
    - Cord Blood Collection Ex Utero or In Utero
- **Shipment of Cord Blood from Collection Site to CCBB**
    - **Shipping Cord Blood from Local Collection Site**
    - **Shipping Cord Blood from Remote Collection Site**
    - **Shipping Cord Blood from Non-fixed Site**
- **Receipt at CCBB Processing Laboratory and Initial Qualification**
    - **Receipt of Cord Blood at Processing Laboratory**
    - Pre-processing Sample Count (Total Nucleated Cell Count)
- **Processing**
    - **----------(b)(4)----------**
- **Cryopreservation**
    - **----(b)(4)----- Method**
- **Long-Term Storage**
    - **BioArchive**
    - **Controlled Rate Freeze and Regular BioArchive Use**
    - **Retrieval of Product**
    - **BioArchive Monitoring and Maintenance**
- Registry Inquiries
- Potency Assays and Confirmatory Typing
- **Shipment of HPC-C Product to Transplant Center**
- Post-Transplant Follow-Up

Cord Blood Collection

Harvesting of cord blood from placentas of mother/donors can be performed at specified collection sites either locally or remotely or at "non-fixed" sites. The cord blood is collected ----------(b)(4)---------- using methods that maximize the collection volume and minimize the risk of microbial and maternal cell contaminations. The collection of the cord blood is performed per approved procedures and by trained personnel.

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

At the end of the collections, products containing a minimum of (b)(4) of cord blood (excluding volume of anticoagulant) are shipped to the CCBB Processing Laboratory per standard procedures.

Cord Blood Collection Validation

The collection of cord blood was validated by a retrospective review of collections and incidence of positive cultures of collections by the staff of the CCBB at Duke after initial validation during COBLT study (Fraser, et al. J Hematotherapy 7:521-561, 1998 and Kurtzberg, et al. Transfusion, 45:842-855, 2005)

16,890 collections were reviewed, 8207 ex utero from the COBLT study (1998-6/30/2001) and 8683 from 7/01/01 to 6/3/06. In the second cohort, 696 collections were performed in utero by MDs. Positive sterility rates, established through COBLT, are targeted at (b)(4). Sterility was tested using a ---(b)(4)--- unit.

The failed sterility rate for the Duke Collections during the COBLT study was 0.79%. Review of the later cohort revealed a sterility failure rate of 0.76%. Sterility is monitored as a QA measure through the Duke Pathology and Pediatrics QA committees (quarterly) and the Duke BMT QA Committee (monthly).

Shipment of the Collected Cord Blood from the Collection Site to CCBB

There are two procedures for post-collection storage and transport of a cord blood unit (CBU). The processes are different to reflect the proximity of the collection site to the

CCBB Processing Laboratory (Local vs. Remote). Details regarding each process are discussed below.

Local Shipping

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Non-Fixed Site Shipping
Shipment of CBUs from a non-fixed site is also considered remote shipping. A non-fixed site is one that is not a regularly collected site, such as a midwife for a home delivery.

Once the collection is completed, the cord blood unit must be stored and shipped in an acceptable temperature range until it is delivered to the processing laboratory. The Non-

Fixed Site Collection Kit is a collection of materials contained in an insulated shipping container (shipper). If the validated temperature range is not maintained, the cord blood unit and the maternal blood samples will be discarded as biologic waste. The procedure for shipment of collected units from a non-fixed site to the CCBB is described in SOP CCBB-COL-015.

The packaging of the collected material should start by emptying the insulated shipping container and removing the insulated lid and foam plug to the side. One Exogel (white) panel is placed in bottom of the insulated shipping container. One absorbent pad is placed on top of the first Exogel panel. The Ziplock bag with Cryopak gel filled pouch, maternal samples, cord blood unit and activated temperature logger should be placed into the shipping container on top of the absorbent pad. The second absorbent pad, the second Exogel panel, the gray foam plug, and the silver foil Styrofoam lid should be placed into the shipping container. All completed documents (placed inside the CCBB envelope) should be placed on top of the Styrofoam lid. Lastly, the shipping container should be sealed with the provided packaging tape.

When packaging is completed, the shipping label provided in the collection kit should be securely posted on the shipping container. The container is delivered to the nearest Fed-Ex shipping location within 12 hours of the collection or, if not available, a pick up is arranged with the provided number.

Validation of Non-fixed Collection Site Shipper - Duke Cord Blood Shipper MK II
Duke Cord Blood Shipper MK II (TCP P/N FPU00073) is used for transporting the collected cord blood products from non-fixed collection sites to the CCBB processing laboratory. The shipper is designed to maintain temperature of the product material between ----(b)(4)---- for the entire -(b)(4)- duration of shipping.

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I reviewed the raw data and graphs provided with the validation protocol and the data demonstrates that the product material, when placed within the finalized shipping configuration, maintained between -----(b)(4)----- throughout the entire -(b)(4)- temperature profile.

Receipt at CCBB Processing Laboratory and Initial Unit Qualification

Upon receipt of the CBUs and maternal samples in the receiving area in the Processing Laboratory, receipt is documented on the Shipping Log. If multiple units are received at once, only one unit at a time will be removed and documented as received. Any data loggers are located and turned off. Temperature data are uploaded to a computer and reviewed. The receiving technician follows SOP CCBB-LAB-017 to verify the barcode identity of the donor, verify the identity of the collection site, to inspect the bag(s) for leaks, and to complete the required information on form CCBB-LAB-017(FRM2). Label verification is also performed between the ISBT barcode label on the collection bag, the ISBT label on the collection form, the manila envelope, and the Shipping Log.

If the unit is intact and labeled properly, the Receipt Form is completed and entered into the -(b)(4)- computer database. Working packets containing the paperwork utilized in processing are prepared, and code 128 barcodes are replicated for each CBU. Units are sent into the Processing Laboratory and delivered to the prequalification area. Maternal sample tubes are refrigerated until preparation for shipment to the NTL for infectious disease testing while some will stay at the facility to be processed for storage.

A supervisor is notified if the incoming unit has any issues regarding this label inspection. Labeling issues during the manufacturing process that cannot be resolved result in disposition of the product according to CCBB-LAB-005.

Receipt of CBU from a Non-Fixed Site

Due to the critical nature of the establishment of confidentiality and linkage, only one non-fixed site kit collection Confidential Packet is completed at a time according to CCBB-COL-016 and CCBB-COL-017. When a collection kit is received at the CCBB laboratory, the kit is opened and the donor paperwork, CBU, maternal samples, electronic data logger and shipping label are removed. The collection kit number, temperature logger number and date and time of receipt are noted on the Non-Fixed Site CBU Receiving Log.

Identifiers are removed from the air bill shipping label taken from the top of the shipper and stapled to the same Non-Fixed Site CBU Receiving Log. Consent to participate in a research study must be present within the package and completed with donor initials on each page and donor's signature and the date when consent was signed on the last page. Once the paperwork is received, a Confidential Packet is created. The mother/donor's name and date of birth is written on the inside flap of the Confidential Packet envelope that arrived with the collection kit. If provided by the donor center, a maternal label may be used for this purpose provided that the name on the label matches the name on the informed consent and the Volunteer Cord Blood Identification Form (VCBDIF).

The date and time of the CBU collection is confirmed. If the receipt is greater than --------(b)(4)-- after collection, CBU will be deemed expired and is ineligible for banking. If the consent to participate in research is not signed, if donor identity is not confirmed on all forms, if signatures are not present, or if maternal samples do not meet requirements per CCBB-COL-025, the CBU and maternal samples will be discarded into biohazard waste per CCBB-LAB-005.

Criteria for Exclusion of Unit

When the cord blood unit is received at the laboratory it undergoes screening to determine eligibility for further processing. To be eligible, it must:

1. Be --(b)(4)-- old since collection
2. Be labeled and packaged properly
3. The kit unit, maternal blood samples and paperwork are labeled with the maternal hospital label when shipped to the CCBB.
4. Have a volume (b)(4)
5. Have documentation of completion of collector (MD or midwife) training
6. Have completed paperwork, including signed consent
7. Have a pre-processing sample total nucleated cell count --(b)(4)-- cells

If elements 1-6 are present, a barcode label is assigned to the CBU and it is sent to processing for a total nucleated cell count (TNCC). If the TNCC is --(b)(4)-- cells, the unit is fully eligible and CBU is processed. If the CBU does not meet the criteria listed 1-7 above, it is disposed.

The exclusion criteria for CBUs from non-fixed sites are the same as those for fixed CCBB sites. However, the following additional exclusions apply:

- Units that arrive more than 48 hours after collection will be rejected
- Units will be rejected if donor follow-up cannot be completed within 60 days of CBU receipt
- If the mother/donor identity cannot be verified, the unit will be rejected
- If any information from the confidential packet cannot be completed or verified, the unit will be rejected

Processing

As the collection bag and its associated materials are moved from the receipt area into the processing lab, the bag is maintained in such a way as to keep it away from coming into contact with another CBU and to keep it free from possible contamination by equipment and work surfaces.

During processing, only one CBU is handled by any technician at a time. ----------
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Shipment to Transplant Center

Shipment of the frozen CBUs is done with dry shippers. CCBB has a system for tracking each of the dry shippers through its serial number. This identifying information is used on shipping documents, on quality control documentation, on downloaded data logger results, and to keep track of which shippers are currently in use.

Prior to Shipment

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Day of Shipment

On the afternoon that the HPC-C product is to be shipped, the dry shipper is emptied of any remaining liquid nitrogen. The stainless steel canister holding the HPC-C product is removed from its designated location in the BioArchive storage system using a ----(b)(4)---- retrieval cartridge and a retrieval cassette. Once it is removed, the HPC-C product is immediately placed in the vapor phase of another liquid nitrogen filled container for viewing. The cryobag is removed from the steel canister, and two separate technicians examine the ISBT barcode on the cryobag against the release paperwork to ensure that the proper unit has been retrieved from the freezer. The cryobag is examined for any malformations, cracks, or broken seals. Additionally, the product is inspected, and label verification is performed according to CCBB-DIST-027.

At this point, the expiration date label is tied directly to the steel canister holding the HPC-C product cryobag. The expiration date will be determined from the approved expiry period and the date of manufacture of the HPC-C.

The entire canister (including the expiration date label) is then placed back into the retrieval ----(b) (4)---- insert. Digital pictures of both sides of the cryobag are taken (front and back sides) for documentation of the appearance of the HPC-C prior to shipment.

These pictures are printed, and copies are maintained in the manufacturing record. After the digital pictures are taken, the HPC-C product is returned to the steel canister.

If additional reference samples were requested to be shipped with the unit, the barcodes for these samples are verified, and the vials are placed into a (b)(4) vial box. The box is labeled with an ISBT barcode and the list of contents on the lid. The HPC-C product (and the sample box, if applicable) is then placed into the dry shipper. Another digital picture is taken of the unit and sample box, if applicable, as they are loaded into the dry shipper. The photo also includes the dry shipper serial number to capture which dry shipper was used. The electronic data logger is seated into the lid of the dry shipper, initialized and activated as defined in CCBB-DIST-012. A technician will then read the temperature on the data logger to ensure that the starting temperature is ≤ -150 °C.

After making a copy of the "Packing Information Sheet," this form (CCBB-DIST-019) is faxed over to the receiving facility. The following information is placed into an addressed envelope:

- Carolinas Cord Blood Bank Packing Information
- AABB Circular of Information
- Package insert/label
- Transplant center receipt instructions (CCBB-DIST-022)
- Transplant center thawing instructions (CCBB-DIST-028)
- Instructions on reinfusion of thawed stem cells for transplantation (CCBB-DIST-016)
- NMDP Form 600 Receipt of Cord Blood Unit
- NMDP Cord Blood Unit- Product Insert
- CIBMTR Hematopoietic Stem Cell Transplant (HSCT) Infusion Reporting Form
- Four CBU bar code labels
- Final Demand 128 tie tag for CBU
- Return air bill (if applicable)

This envelope is then sealed and placed on top of the data logger lid. The dry shipper is closed and tied with zip ties. A zip-tie is used to secure the lid to the dry shipper. A yellow NMDP provided zip tie containing the HPC-C product ISBT barcode, NMDP recipient ID, and NMDP CBU ID is also used to seal the lid to the dry shipper. This tag is used for verification purposes at the transplant center, but it also serves as a tamper resistant marker to ensure that dry shipper was not opened during shipment. The dry shipper must be labeled with the following information:

- date of distribution
- shipping facility name, address, and phone number
- receiving facility name, address, and phone number
- identity of person or position responsible for the receipt of the shipment
- statement "DO NOT X-RAY"
- statement "Medical Specimen" and "Handle with Care"
- statement indicating "Cord Blood for Transplantation"
- shipper handling instructions

The shipper is picked up by the courier at the CCBB Processing Laboratory, or it is left at the designated drop off point for the appropriate courier.

Receipt of the Shipper at Transplant Center
Upon receipt of the dry shipper at the transplant center, the appropriate person removes the tie tags and opens the manila envelope containing the packing information and the package insert. The NMDP Receipt Form (Form 600) is completed to ensure that the ID on the HPC-C product and the recipient ID are consistent and match what is printed on the Packing Information Sheet. The transplant center removes the HPC-C product and inspects it. The cryobag is then placed into either vapor phase or under liquid nitrogen for storage until thaw for infusion. The transplant center is to document and communicate any issues with the condition of the HPC-C product upon receipt through NMDP Form 600.

After the HPC-C product is safely stored, the condition of the dry shipper and the temperature monitoring device are inspected. The CCBB contact person should be notified if there is any indication that the product was damaged or exposed to temperatures > -150°C. Once completed, the NMDP Receipt Form (Form 600) is faxed to the NDMP and to the CCBB Processing Laboratory.

Return of the Empty Dry Shipper
The CCBB Processing Laboratory requests that the transplant center returns the dry shipper (using the return shipping label, if included) as quickly as possible. On the day that the shipper is sent back to the CCBB Laboratory, the transplant center is asked to notify the appropriate CCBB contact person so that he/she can be expecting its arrival. Upon return delivery of the empty dry shipper to the CCBB Laboratory, all courier information is removed.

The information from the data logger is downloaded, printed, and filed according to standard procedures. The expected temperature range is from ≤ -150°C to (b)(4). Any temperature issues are immediately brought to the attention of the Operational Manager of the CCBB Processing Laboratory. If a temperature issue is confirmed, the NMDP is also notified. The temperature data and NMDP Form 600 for each HPC-C product are reviewed and added to the CCBB manufacturing file for that HPC-C product. The HPC-C file is then submitted to the laboratory supervisor for review and signature, which is then returned to the Operations Manager for refiling.

After receipt, the empty dry shipper is inspected for damage and then placed back with the dry shippers that remain available for use. Each dry shipper is cleaned between uses as needed, and annually, each shipper undergoes a full decontamination. Any damage that occurred to the dry shipper during shipment to or from the transplant facility is reported to NMDP.

Validation of Shipping and Handling of HPC-C Product to Transplant Center Dry Shippers

Cryopreserved umbilical cord blood units must remain in a frozen state throughout shipment to the transplant facility. Dry shippers are designated for the safe transportation of biological samples at cryogenic (≤ -150°C) temperatures. They employ ----------
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----------(b)(4)----------

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A fully charged dry shipper must be capable of holding a minimum temperature of ≤ -150°C for a period of 48 hours beyond the expected time of arrival at the transplant facility. While all shipments of CBUs are prepared for overnight delivery to the recipient site, unpredictable delays in shipping could occur after the HPC-C has left the bank. Therefore, all shippers are validated for (b)(4) of temperature stability.

Validation data submitted to the BLA in Section 3.2.P.3.2.1. I reviewed the temperature graphs and data submitted and it is acceptable. The data demonstrate the dry shippers can be held at ≤ -150°C for a maximum of (b)(4). Data loggers are inserted in each shipment to provide the data to confirm the dry shippers held the appropriate temperature throughout the time of shipment.

Each dry shipper also undergoes (b)(4) quality control testing by appropriate CCBB personnel. Specifically, the staff checks the integrity of the dry shipper container, and standard procedures are followed to determine if each dry shipper can successfully maintain the established temperature (≤ -150°C) for a period of at least -(b)(4)- beyond the expected arrival time to the designated facility. Each dry shipper is labeled with the number of days that the shipper is validated to maintain adequate temperatures. This testing is documented on CCBB-DIST-012 (JA2).

Container Closure System
All containers and closures that are in direct contact with the HPC-C products (both collection and processing) are purchased sterile. The table below summarizes the containers and closures that come into direct contact with the collected cord blood and/or the HPC-C product. A more detailed description of the container follows after the table. The final storage container for the HPC-C product, the cryobag, is part of a closed system kit that is used to process each cord blood unit (CBU).

As part of the Quality Program for the production of HPC-C products, all containers and closures are confirmed to meet specified requirements. All containers and closures are initially quarantined and continuously monitored upon delivery and receipt according to COMM-QA-001. A FIFO (first in, first out) policy is used for distribution of the materials and the company supplied expiration date is not exceeded. All supplies must be stored at an appropriate temperature in a safe, sanitary, and orderly manner.

Since the container closure systems are either FDA approved or 510(k) cleared, the Agency does not expect CCBB to perform additional testing such as leachables / extractables.

Summary of Container Closure Systems Used During CCBB Manufacturing of HPC-C Product

Container/ Closure	Supplier	Product Code	Supplier Address	Documentation Present (Compatibility or NDA, 510K or DMF referenced)
Cord Blood Sterile Collection Bag	---(b)(4)---	---(b)(4)---	----------(b)(4)----------	----------(b)(4)----------
---(b)(4)----Processing Set	----------(b)(4)----------	---(b)(4)---	----------(b)(4)----------	----------(b)(4)----------
Freezing Bag	---(b)(4)---	---(b)(4)---	----------(b)(4)----------	----------(b)(4)----------
Overwrap Bags	-----(b)(4)-----	--------(b)(4)--------	----------(b)(4)----------	----------(b)(4)----------
Stainless Steel Storage Canister	ThermoGenesis	-------(b)(4)--------	ThermoGenesis Corp. 2711 Citrus Road Rancho Cordova, CA 95742	----------(b)(4)----------

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Sterile (b)(4) Collection Bag Validation
This validation demonstrated that the (b)(4) sterile collection bag (b)(4) is not inferior to other bags used for the collection of cord blood stored at the CCBB. The validation tested whether products collected in the new bag yield the same results as those collected into the previously used bag, specifically comparing % recovery of TNC, CD34, and (b)(4).

Each unit will be evaluated for post processing TNCC, post processing viability, % recovery of nucleated cells, ----------(b)(4)------, total CD34+, ---------- -----(b)(4)----------.

The acceptance criteria stated that the units must be within (b)(4) of historical controls of CBUs of similar volumes with regard to (b)(4), CD34, viability and TNC recovery.

The results of the validation are included in the submission and CCBB concluded that the data do not support a conclusion that the (b)(4) sterile collection bag ----------(b)(4)---------- is inferior to other collection bags with regards to pre-processing TNC count. Of other CBU characteristics explored, only ----(b)(4)---- appears to be inferior with use of the (b)(4) sterile collection bag, ----(b)(4)----. CCBB accepted the use of the (b)(4) sterile collection bag --(b)(4)--.

---(b)(4)---- Processing Set- --(b)(4)--

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

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Freezing Bag – ---(b)(4)---

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

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Overwrap Bag- -------(b)(4)---------

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-------(b)(4)--------- Overwrap Validation

The overwrap was subjected to various tests to determine its acceptability for use in the freezing of the CBU in the BioArchive system. The tests consisted of the following:

- The overwrap was visually inspected by ----(b)(4)----- for defects, pin holes, cuts, or incomplete seals.
- Thermal Cycle Testing to determine if the same overwrap can be used more than one time. Specifically, can an overwrap be put on a unit, frozen, remove the overwrap, and then use the same overwrap on the unit when it is placed back into LN_2.

Of the (b)(4) overwraps inspected by ----(b)(4)---, no rejected bags were found during the inspection.

The (b)(4) overwrap bags were used to overwrap -(b)(4)- freezer bag samples filled with 25ml of saline/DMSO/Dextran 40 mixture. After the first (b)(4) were tested, the samples were thawed, the overwraps removed, and then overwrapped again with (b)(4) more overwrap bags, and retested. This process was repeated a third time using ---(b)(4)--- freezer bags to complete testing of all (b)(4) overwrap bags.

For each (b)(4) bags tested, they were placed in canister 6-16-062 and stored in LN_2 for a
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----------(b)(4)----------
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The Initial freeze store and retrieve had no failures for all (b)(4) bags tested. During second freeze/store cycle, two samples failed due to puffiness of the overwrap bag. One sampled

failed during testing of the second (b)(4) overwrap bags. The canister was noted to be open. The second sample failed during testing of the last (b)(4) overwrap bags. The canister opened up during retrieval and the sample fell to the bottom. The canister opened before it was exposed to LN_2 gas suggesting that the canister was never fully closed after the first retrieve, examination/handling, restore. It can not be precisely determined when the two bags failed - during the handling after the initial retrieve and successful inspection or during handling after the second retrieve. Either way it suggests it happened during handling.

CCBB concluded that the data support the overwrap bags acceptance as a one time use only bag. Because the overwrap bags failed during the second retrieval and inspection / handling process, this suggests that the material should not be reused in the event the wrong sample is retrieved (i.e. handled and then restored without replacing the overwrap bag). If a sample is retrieved and handled by the user, the overwrap should be removed from the sample, and replaced with new before being restored.

Stainless Steel Storage Canister- Thermogenesis
The storage canisters from Thermogenesis (------(b)(4)------) are specially-designed stainless steel containers that hold samples for storage in the BioArchive freezing and storage system employed by the CCBB Processing Laboratory. Each non-sterile canister arrives individually packaged in a zip-lock baggie. The thermal properties of the canister enhance heat transfer during the freezing process and protect the unit from uncontrolled warming when removed from the BioArchive system. The HPC-C product cryobag remains in this metal canister through shipment to the transplant center, as extra protection for the cryobag during transport.

Methods Validation/Verification
Infectious Disease Test Methods
DMPQ does not review ID testing validation / verification

Other Test Methods
OCBQ/DBSQC would typically review Sterility testing validation; however, for cord blood units, the Product Office will now be responsible for this review.

Validation Results
The Product Office is responsible for review of testing validation results.

Labeling
DMPQ does not review labeling.

Specific Systems
Water System
Deionized Water System

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

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Liquid Nitrogen Cryostorage System

Liquid nitrogen cryostorage units for the long term storage of frozen HPC-C products are located in Rooms ------(b)(4)------ of the North Pavilion facility. HPC-C products are stored immersed in liquid nitrogen in Thermogenesis BioArchive (------(b)(4)------) cryogenic storage systems. ----------
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Particulate Monitoring

Total particulate environmental monitoring is performed in the manufacturing area on a continuous basis with a particle counting system (----------(b)(4)----------) with a single probe located in the approximate center of the Processing Laboratory. The probe is located in a high traffic area, ----------(b)(4)----------.

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Microbial Monitoring

To assess the effectiveness of the facility disinfection processes, microbiological analysis of airborne microbial bioburden in the CCBB Processing Laboratory was conducted in December 2010.

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(b)(4)

Results indicated that very low (-------(b)(4)------) levels of fungi were cultivated in only ---(b)(4)--- samples obtained over the two different monitoring days. In the bacterial samples, the quantity of bacterial isolates was also very low. The bacterial species isolated were low levels of non-pathogenic flora associated with human skin (coagulase negative Staphylococci, viridians Streptococci) or soil (Bacillus). The total isolates cultivated in the low and high activity samples were comparable.

Per CCBB, Environmental microbial monitoring described above will be performed on a --(b)(4)-- basis to ensure that their prospective cleaning plan described above continues to provide an appropriately clean environment for the processing of CBUs.

Routine Environmental Monitoring
CCBB has agreed to the following routine environmental monitoring for the Biological Safety Cabinets (BSCs):

All hoods used for manufacturing will be monitored on a --(b)(4)-- basis.

Viable monitoring will occur --(b)(4)-- per hood under dynamic conditions.

Non-viable particle monitoring will occur --(b)(4)--, at a minimum, for each hood under either static or dynamic conditions.

The following Alert / Action Levels have been established for the laboratory and the BSCs:

(b)(4)

(b)(4)

Facility Controls
After collection, the CBU is moved to the CCBB Processing Laboratory where it is handled using aseptic technique and manipulated either using functionally closed systems or in a --(b)(4)-- biological safety cabinet. Details about the controls and monitoring that occur during collection and processing of a CBU are provided below.

Collection
Collection of cord blood occurs in a specific collection room at each hospital site associated with the CCBB or by a trained care provider in the delivery room. Access to each of the collection rooms is restricted through keyed entry, and the door remains closed at all times that someone is not entering or exiting. To help ensure the collected cord blood does not become contaminated, each collection room is cleaned daily and at

the end of each collection shift per CCBB-COL-030. Additionally, trained personnel collect cord blood while wearing a disposable gown secured in the back, at least two pairs of gloves, and protective face wear.

Daily cleaning of the collection room occurs by Environmental Services per site specific Environmental Services Cleaning Specifications. This cleaning is documented on CCBB-COL-032 (FRM 1). Each collection room is be cleaned by the site's Environmental Services by (b)(4) each day. In the event the room has not been cleaned by this time, the Environmental Services supervisor is contacted. If someone from Environmental Services is unable to clean the room, the collection staff at that site performs the daily cleaning. Both Environmental Services and collection staff are responsible for checking sharps containers in the room. Site specific policies are followed to replace the container with an empty one when the previous container is no more than --(b)(4)-- full. The collection room is never cleaned by Environmental Services during a cord blood collection.

At the end of each collection shift, trash is removed and disposed of per site specific policies. Biohazardous waste is emptied and disposed of per site specific policies. Prior to each collection, the collection area and related equipment are cleaned per CCBBCOL-030 and CCBB-COL-008.

Additionally, instruments that are used directly in the production or measurement of CBUs must be cleaned, inspected, and confirmed to be in good working order on a (b)(4) basis. Examples of this type of equipment include scissors and the rocker scale used for the cord blood bag during collection.

Processing

Processing of each CBU occurs at the CCBB Processing Laboratory, which is located in a manufacturing suite at Duke University Medical Center. Access to this room is restricted to those with card access only. Personnel in the Processing Laboratory wear clean lab coats and at least one pair of gloves in all of the manufacturing areas, including receipt. Each staff member has multiple lab coats, which are only to be worn when working with CBUs and/or samples.

To minimize the risk of contamination to HPC-C products processed in the CCBB Processing Laboratory, the whole processing procedure is performed in a clean environment, which is achieved using aseptic technique for all product processing. Manipulations that require sample removal (i.e. obtaining samples for cell counts, viability, ----------(b)(4)----------) that involves means that do not use a functionally closed system, are performed in a ----------(b)(4)----------, which is cleaned before each use with --------(b)(4)--------- to help reduce the likelihood of product contamination. ----------
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----------(b)(4)----------

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Facility Cleaning

To assure maintenance of aseptic processing conditions, a (b)(4) cleaning and decontamination of the Processing Laboratory is accomplished per standard procedures (CCBB-COL-008 and CCBB-LAB-042). Additionally, a qualified vendor has been hired to perform --------(b)(4)---------- disinfection of the CCBB Processing Laboratory has been implemented. This disinfection employs the use of --------(b)(4)--------- to disinfect the surfaces in the Processing Laboratory, including sinks, biological safety cabinets, counters, cabinets and other surfaces. To ensure that all Laboratory contaminants remain at an acceptable level, ----(b)(4)------ environmental monitoring is performed to assess the efficacy of these cleaning procedures.

Disinfectant effectiveness studies were not performed for the cleaning solutions or the cleaning process. According to OCBQ, CCBB only has to have their SOPs reflect what is written on the back of the cleaning agent and that will be acceptable.

Technicians within the lab decontaminate work surfaces with ----------(b)(4)---------- as appropriate for that particular surface and per CCBS-LAB-042. This cleaning must be done daily after completing all procedures, immediately after surfaces are noticeably contaminated, or after any spill of blood or other potentially infectious material. In addition, the following disinfection and decontamination is performed by the CCBS Processing Laboratory staff:

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

Appropriate Duke personnel empty and/or remove the large biohazard trash, remove full sharps containers, and non-biohazard trash (b)(4). Additionally, the Environmental Services staff sweep and wet mop the CCBB Processing Laboratory floors (b)(4). Any non-working surfaces (such as the top surfaces of the refrigerator/freezer unit) that might contribute to overall lab contamination are cleaned by the Environmental Services personnel -(b)(4)-.

All of the SOPs referenced above were included in the BLA submission. I reviewed all of the procedures and found them to be acceptable.

Overall Disinfection of Facility and Equipment Exterior Surfaces
Beginning in August 2011, an enhanced facility disinfection program with a qualified cleaning vendor was initiated. This new cleaning plan incorporates procedures representative of typical biologics industry practice that employs the ----------
----(b)(4)----.

To ensure that this cleaning plan continues to provide proper disinfection of the facility and equipment, a -(b)(4)- microbial monitoring will be instituted.

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These disinfection practices are industry standard. --(b)(4)-- microbial monitoring will be used to continually evaluate the disinfection process.

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Decontamination of Equipment Work Surfaces
Decontamination of equipment work surfaces associated with line clearance to prevent cross contamination between CBUs is described below for both collection and processing procedures.

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Facility Access Control
Unauthorized access is controlled by card key readers at entrances to the building and at entrances to the Carolinas Cord Blood Bank Processing Laboratory.

Storage areas for the BioArchive equipment are also accessible only through card access. The card reader outside of the laboratory requires card access at all times. Additionally, a camera phone is utilized to identify visitors at the door of the Processing Laboratory. All visitors are escorted by an employee in and out of this area.

Computer Systems
The Carolinas Cord Blood Bank (CCBB) utilizes a few different computer systems to control critical manufacturing processes. There are major systems that store data about the cord blood unit (CBU) itself and minor systems that are necessary for operation of critical equipment. The major system used by the CCBB is the -------(b)(4)---------, created by the ----------(b)(4)----------. The other major system housing CCBB data is the National Marrow Donor Program (NMDP) database, CordLink, which houses the complete set of data for products listed on the NMDP "Be the Match" Registry. Both the --(b)(4)-- and CordLink systems are data systems that store information on cord blood units (CBU) and/or HPC-C products as applicable.

The --(b)(4)-- system records results of donor eligibility screening and testing, in addition to serving as the structure for all processing, cryopreservation, and storage information/test results for each CBU. The CordLink program also contains this information for each HPC-C product that is determined to be acceptable for release from quarantine and upload to the NMDP registry. This CordLink site serves as the selection and registry site sponsored by the NMDP.

During processing of a CBU, there are additional steps that are ---(b)(4)------. The BioArchive from ThermoGenesis and the ----------(b)(4)---------- are two critical ------(b)(4)--- instruments that are utilized to manufacture each HPC-C product. The ----------(b)(4)----------. The BioArchive serves as the system for -----(b)(4)----- freezing, storage, and retrieval of each HPC-C product. In addition, the --------(b)(4)-------- cell counter to perform electronic analysis and storage of sample runs as a record of the results (CCBB-LAB-039).

The CCBB also scans all confidential files on a standard scanning set-up which is not linked to any other computer systems but is backed up manually.

All of the above computer systems were developed by the relevant contractor / manufacturer and are continually supplied by these vendors. Details regarding the software platforms that supply each of the above functions are provided below.

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CordLink
The CordLink application is provided by and supported through NMDP. This system is utilized by the CCBB and all public cord blood banks participating in the National Cord Blood Inventory (NCBI) as a data registry to feed the NMDP donor search system. This system is not unique to the CCBB; the NMDP requires all banks to utilize this mechanism to coordinate product requests from transplant centers. CCBB electronically stores information on each CBU in the --(b)(4)-- system. Once the CBU is approved for release, much of this information is uploaded through an electronic link created by --(b)(4)-- and stored in the NMDP CordLink application.

CordLink is an application provided by the NMDP to help organize and store the large amount of information required to maintain a cord blood unit (CBU). The information stored includes HLA typing, processing details such as type of processing, type of cryopreservation bag, additives, conditions of long term storage, cell counts, CD34+ cell,

(b)(4) and sterility results, hemoglobinopathy screening, ABO/Rh typing, baby gender, HLA typing, maternal infectious disease testing results (IDMs) and maternal responses to the Family Medical History Questionnaire (FMHQ) and Maternal Risk Questionnaire (MRQ), e.g. donor screening results.

The CCBB also utilizes CordLink to manage search requests, confirmatory typing requests, and results and requests to ship units to transplant centers facilitated through the NMDP.

The CCBB electronically uploads qualified CCBB products to the NMDP Registry in an ------(b)(4)-------- from collection after review and qualification of all critical elements. Released units are uploaded to CordLink (directly through ----------(b)(4)---------- following an internal review by three different individuals within the CCBB. Once in CORD Link, the application allows CCBB to control a product's availability through the assignment of Local Registry Status. The NMDP determines availability with the National Registry Status based on the results from Qualification Service in the CORD Link application, and/or by active search requests. The National and Local Registry Statuses track availability status within the NMDP systems.

The CCBB receives notification through the CordLink application for NMDP facilitated search requests. Once a search request is made for a CBU, the CBU is removed from other searches (i.e. It is not visible to other transplant centers) until the request is resolved. The CCBB tracks activity and tasks associated with a specific CBU/recipient pair in the Search Folder of CordLink. Searches are categorized by different stages: Confirmatory Typing, Held (allowing the transplant to reserve a CBU), and Order. The History Table in CordLink allows the CCBB to track and monitor all activities associated with a single CBU, from entry into the system through shipment or infusion.

Modifications and new entries in the CordLink application are reevaluated by the Qualification Service and if necessary the classification status would change. The Classification Status change is provided to the NMDP Search Coordinator and transplant center electronically through NMDP systems. Changes are also impacted by search activity. As transplant centers initiate and terminate search requests for CBUs through the NMDP systems, the National Registry Status and search availability for other patients is constantly monitored and identified. CCBB receives electronic notification of all changes in activity initiated by transplant centers.

There are four layers of security in the CordLink application:

- Secure HTTP or Secure Socket Layer (SSL)
- SecurID card
- Data server firewall
- Application level security

The NMDP maintains system security by encrypting the Internet connection with Secure Socket Layer (SSL) technology. The system requests a special ID code at time of login, along with a User Name and Password. The SecurID card provides the user with a unique

random identification number every 60 seconds based on an internal clock. The data server is protected by a firewall that verifies the User ID and SecurID codes for that user.

In addition, each User ID has rights within the application defined by the cord blood bank coordinator. These rights allow users to view or edit data within the software application. The system is dynamic enough that the cord blood bank coordinator can offer screen-viewing privileges without editing privileges. To ensure confidentiality, only those NMDP staff members directly supporting cord blood bank activities will have access to cord information at the NMDP Coordinating Center. Additionally, the application is designed to let the CCBB (and other banks) arrange different security access levels for different user types. The CCBB also has the authority to remove access as needed.

Validation of (b)(4) Results Transfer to --(b)(4)--

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Cross Contamination / Contamination Precautions and Training

After collection, the CBU is moved to the CCBB Processing Laboratory where it is handled using aseptic technique and manipulated either using functionally closed systems or in a ----------(b)(4)----------. Details about the controls and monitoring that occur during collection and processing of a CBU are provided below.

Collection

The most important mechanism used to prevent contamination /cross-contamination is to handle only one CBU at a time. This, and ensuring area clearance around the collection stand prior to use, also minimizes the possibility of cross-contamination. Additionally, each collection bag is carefully labeled, and only one set of labels is out in the collection area at a time. Prior to packing the collection bag for transport to the Processing Laboratory, the labels on the bag are verified with those on the associated paperwork and with the remaining labels in the bag.

To help ensure the collected cord blood does not become contaminated, prior to each collection, the collection area and related equipment is cleaned per CCBB-COL-030 and CCBB-COL-008. This cleaning is documented on the appropriate forms. Additionally, trained personnel collect cord blood while wearing a disposable gown secured in the back, at least two pairs of gloves, and protective face wear. After collection, the cord

blood bag is inspected for any leaks or tears. If any are detected, the CBU is disposed of according to standard procedures.

In-process controls performed at this step in the manufacturing process to prevent or identify contamination consist of a careful inspection of all equipment and materials prior to use. Specifically, ----------
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---(b)(4)---

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Training

In order to ensure the staff is thoroughly trained in aseptic techniques needed during the collection process, a specific training plan is followed according to CCBB-TRN-002. Each new collection technician starts by reading the SOPs and completing an initial ----(b)(4), intensive training with a designated trainer who is a collection specialist. This new staff member is trained by watching a senior collection staff member and then practicing on units that cannot be banked. Training units, disposed of at the collection site, are used for practice until the new staff is able to collect independently.

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Cord Blood Unit Processing
Processing of each CBU occurs at the CCBB Processing Laboratory at Duke University Medical Center. Personnel in the Processing Laboratory wear clean lab coats and at least one pair of gloves in all of the manufacturing areas, including receipt. Each staff member has multiple lab coats, which are only to be worn when working with CBUs and/or samples.

As soon as a cord blood collection bag arrives at the Processing Laboratory, it is inspected to ensure that it contains no leaks or tears. If issues with the integrity of the bag are detected, the sterility of the HPC-C product is compromised and this unit would not undergo further processing.

As the collection bag and its associated materials are moved from the receipt area into the processing lab, the bag is segregated in such a way as to keep it away from coming into contact with another CBU and to keep it free from possible contamination by equipment and work surfaces.

The most important mechanism used to prevent cross-contamination during processing is that only one CBU is handled by any technician at a time. By only allowing one CBU within the work area at a time and by ensuring area clearance of each processing workstation area prior to working with another CBU, the likelihood of cross-contamination is minimized. Standard procedures for reducing cross-contamination and mix-ups are outlined in CCBB-LAB-004.

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

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

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During cord blood processing, numerous checks and in-process controls are in place to help reduce cross-contamination between CBUs. First, label verification must be performed on any labeled product, paperwork, and/or labels that are used during critical

steps in the process. These critical steps include ----------(b)(4)----------(as detailed in CCBB-LAB-017 (FRM2), CCBB-LAB-022 (FRM l) and CCBB-LAB-024 (FRM l). This label verification ensures that all products and associated materials are labeled correctly throughout the manufacturing process.

Gloves are to be worn at all times during the manufacturing process when any sample or product is handled. Gloves are ----------(b)(4)----------. Trays and bins are also used to maintain product separation during processing and while moving the CBU from one processing station to another. These trays and bins are also used to transport any samples (and accompanying sample containers) during processing. The paperwork associated with each CBU is located in a folder, which is maintained with the tray/bin during transport between stations.

Area clearance checks and related disinfection are performed between units at each work station during processing and cryopreservation, and these processes are documented on the manufacturing record, CCBB-LAB-022 (FRM 1) and CCBB-LAB-024 (FRM 1). Area clearance steps are posted at each workstation to assist technicians with the proper steps for these checks.

Additionally, any equipment that comes into contact with a CBU during processing is disinfected with -------(b)(4)------- between uses (CCBB-LAB-042). ----------(b)(4)----------.

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

In the event that a CBU leaks or spills during processing, production at that station is halted until the workstation can properly be decontaminated. ----------(b)(4)----------.

Any HPC-C which screens positive in sterility testing is discarded (CCBB-LAB-028). Any HPC-C products in which the maternal donor testing screens positive for syphilis, HIV, HCV, West Nile Virus, Chagas Disease, or HBV (by NAT or Hep B surface Ag) are removed from storage when the test result is received and discarded per CCBB-LAB-005. HPC-C products that screen positive for HTLV, CMV, or HBC are only removed if confirmatory testing verifies that the results were in fact a true positive. Any units where the maternal donor is screened or confirmed positive for syphilis, HIV 1,2,O, Hepatitis C,

Hepatitis B, HTLV I/II, West Nile Virus, Chagas Disease are not listed on the donor registry. Units positive for CMV (b)(4) are not listed on the donor registry.

Training

In order to teach laboratory staff about aseptic manipulations during cord blood processing, a specific training module is followed. ----------(b)(4)----------.

Each new processing technician starts by reading relevant SOPs and completing an initial intensive training with a designated trainer. The new staff member is first trained by watching a senior staff member at the applicable station in the Processing Laboratory. After observing the proper procedures, the new technician is observed by a certified trainer during every processing procedure that he or she performs to ensure all pertinent and necessary steps are being followed strictly to procedure. The trainer may sign off on a new trainee once he/she has independently completed ----------(b)(4)----------. Special attention is paid to aseptic technique and any steps that may compromise the sterility of the CBU. This training plan and the results of the training are documented.

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

Assurance is on-going, and any issues that arise (including unexplained positive sterility tests) require immediate action.

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

Corrective action, in the form of re-training, must be initiated, completed, and documented per each procedure's training document. Documentation of successful completion of re-training must be completed before the staff member is once again released to task and allowed to independently perform the procedure or task. In addition to this annual competency, the Laboratory Supervisor makes a constant effort to observe staff processing CBUs to ensure that proper procedures and techniques are always being employed. This type of oversight helps catch any minor issues or concerns that may arise.

Periodic review of Sterility Results to Indicate Possible Training Issues

The manufacturing files for all CBUs that test positive in the ----(b)(4)---- sterility test are periodically reviewed by Quality Assurance to determine if there are any technicians who may have issues with sterile technique. Although it is difficult to directly correlate a

positive ----(b)(4)---- test with the actions of a specific processing technician (given the station approach to processing and the fact that contamination could have come from collection as well), these results aid supervisors in keeping the staff informed and continuing to ensure that each technician is using proper aseptic technique.

Open Manipulations
Manipulations that require sample removal (i.e. obtaining samples for cell counts, viability, ----------(b)(4)----------) that involves possible open manipulations are performed in a ----------(b)(4)---------- that is cleaned and monitored as described in this review memorandum.

To help reduce the likelihood that an HPC-C product could be contaminated by materials used in the manufacturing process, all containers and tubing in direct contact with the cord blood arrive sterile and are manufactured as single-use components. The integrity of each of these products is also assessed prior to release from quarantine and directly before use to help ensure that no contamination occurs.

After CBU processing, a sample of the CBU is collected for the ----(b)(4)--- test, which is required in order to assure the sterility of a product before listing on the donor registry.

The table below provides a list of the processing steps involving direct contact with the cord blood and the associated entry points.

(b)(4)

Aseptic Manipulations
In order to minimize the likelihood of contamination and cross-contamination of HPC-C products, all staff involved in collection and processing of cord blood are trained in aseptic technique. Staff is trained for all assigned job functions to ensure that each technician can perform the required tasks competently. Incumbent staff must also achieve competency on new tasks and maintain competency on existing tasks.
A description of the aseptic processes and training is included in this review memorandum. Please reference the section titled "Cross Contamination / Contamination Precautions and Training".

In order to ensure that each HPC-C product is not contaminated, sterility testing is performed on each processed CBU using the ----(b)(4)---- System. In short, samples of ----------(b)(4)---------- from each processed CBU are used to inoculate anaerobic and aerobic bottles for culture. Any CBU that yields a positive result for growth are tested in the Duke Hospital Clinical Microbiology Laboratory for further identification and sensitivities. These HPC-C products are disposed of per standard procedures.

Additionally, the manufacturing records for positive HPC-C products are examined by Quality Assurance periodically to elucidate any potential trends with regard to sterility issues during the manufacturing process.

Standard Operating Procedures Submitted per FDA Guidance Document
The FDA guidance document for minimally manipulated cord blood lists standard operating procedures (SOPs) that need to be submitted with the application for performance of the following critical operations. The items in **bold** font are, at least in part, DMPQ responsibility for review.

a. Collection
Maternal screening6 and obtaining informed consent;
Donor eligibility – donor screening and donor testing;
Notification of mothers or their responsible physicians of positive or indeterminate test results according to local or national regulations;
Positive identification of birth mother and donor;
Cord blood collection, **storage, and transport to the processing facility;** and
Criteria for accepting cord blood for further processing.

b. Processing
Plasma reduction, red cell sedimentation, and/or other nucleated cell concentration methods;
Cryopreservation;
Frozen storage; and

Lot release.

c. Selection

Registry listing; and
Search and selection request management.

d. HPC-C Shipping and Handling

Shipping to transplant center;
Thawing and preparation for administration; and
Emergency product recovery in the event of a container failure, including plans for sterility testing of the compromised product and notification of the appropriate individuals and regulatory authorities.

SOP Review

CCBB-COL-009 Post Collection Storage of Cord Blood Unit at the Collection Facility and During Transportation to the Processing Lab

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

The SOP describes how units should be packed into the container. This description matches the packing instructions that were used for validation of the shipper ----------(b)(4)----------.

CCBB-COL-030 (b)(4) Cleaning of Site Collection Rooms

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

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

CCBB-LAB-024 Cryopreservation and Storage of CBU

This 17 page protocol provides detailed steps for the preparation of cord blood for long-term storage. The protocol includes the freezing profile to be used in the BioArchive System and a picture of a typical freeze profile.

CCBB-LAB-017 Receipt of Cord Blood Unit in the Laboratory

The SOP outlines the steps required to ensure correct data tracking and quality assurance when a cord blood unit (CBU) is received by the Carolinas Cord Blood Bank (CCBB) Laboratory from the collection sites.

CCBB-COL-012 Packing and Shipping Cord Blood Unit to Duke University

This document applies to the shipment of all cord blood units intended for clinical use from remote collection sites to the Processing Laboratory at Duke University. All CBU Collection personnel at remote sites need to follow this SOP. The -----(b)(4)----- is an -----(b)(4)---- shipping container (shipper) used to transport cord blood units (CBUs) from a remote collection site to the processing laboratory at Duke University. From the time of collection until the umbilical/placental cord blood unit (CBU) is delivered to the laboratory, it must be stored and shipped in an acceptable temperature range. The temperature range of -(b)(4)- is acceptable.

The SOP follows the shipping validation protocol detailing packing procedures.

CCBB-DIST-012 Procedure for Validation of Dry Shippers
Validation of dry shippers is performed to ensure they are in proper working condition. Selected units are transported from our bank to the receiving facility at the temperature of ≤ -150°C in these dry shippers. The containers should maintain the established temperature for a period of at least (b)(4) beyond the expected arrival time to the designated facility.

Associated Documents:
CCBB-DIST-012 FRM1 Dry Shipper Validation Log sheet FRM1
CCBB-DIST-012 FRM2 Dry Shipper Charge Record FRM2
CCBB-DIST-012 FRM3 Dry Shipper Validation Labels FRM3
CCBB-DIST-012 JA1 Use of Datalogger for Dry Shipper JA1 - This procedure outlines the proper steps necessary to activate, deactivate, retrieve data, and printer data from both the ------(b)(4)------- data logger and the (b)(4) data logger.
CCBB-DIST-012 JA2 Datalogger QC Record JA2
CCBB-DIST-012 JA3 Datalogger Recalibration Stickers JA3

CCBB-DIST-019 CCBB-DIST-019 CBU Shipment Packing Information

CCBB-DIST-025 Overview of Selection, Release, and Transport to Transplant Facilities
This SOP describes the systems for cord blood unit selection, release and transport from the Carolinas Cord Blood Bank at Duke to the transplant center utilizing the unit for their patient.

The bank coordinates the shipping process with the transplant center, meeting the following criteria: (1) A validated dry shipper is charged 24 hours or more prior to planned shipment; (2) Communication channels are established with the transplant center to ensure notification of initiation of shipment from the bank and receipt at the transplant center; (3) a packet of information is prepared to accompany the cord blood unit to the transplant center including the Circular of Information, combination to lock on dry shipper, instructions for storage at the transplant center before transplant, procedure for thawing and infusion, labels, thawing feedback sheet to report adverse events related to thawing and infusion back to the transplant patient and contact information for assistance from the bank.

The transplant center receives the unit and stores it in vapor or liquid phase of liquid nitrogen until the day of transplant. On the day of transplant, the unit is thawed, sometimes washed (at the discretion of transplant center) and infused.

Reactions to infusion within the subsequent 24 hours are scored and reported to the bank. Recoveries of nucleated cells, viable cells, CD34 cells and CFUs are enumerated at the transplant center and reported back to the bank. Microbacterial cultures of the infused product are also obtained by the transplant center and reported to the bank.

CCBB-DIST-027 Shipping Cryopreserved CBUs to Transplant Centers
The purpose of this procedure is to outline the steps involved in preparing, packing, and shipping cryopreserved umbilical cord blood units to be used for transplantation in a dry shipper.

Associated Documents:
CCBB-DIST-027 FRM1 Dry Shipper Outer Label for CBU Shipments FRM1
CCBB-DIST-027 FRM3 CBU Shipment Delivery Address Form FRM3

Critical Raw Materials
Critical raw materials used in the cord blood manufacturing process are Hespan and DMSO. Per CCBB, the raw materials are evaluated by initial qualification and regular evaluation of suppliers. Additionally, critical materials are initially quarantined and continuously monitored upon delivery and receipt according to COMM-QA-001. Materials are used according to FIFO (first in, first out). All materials are stored at an appropriate temperature in a safe, sanitary, and orderly manner. Any material that is not used prior to their expiration date is discarded in an appropriate manner. Additionally, these materials are all chosen for use in a manner such that the lot numbers with the shortest time to expiration are used first.

Information regarding two critical materials (Hespan and DMSO/Dextran) used during the cord blood manufacturing process, are provided in the table below.

Critical Materials for Cord Blood Processing

Material	**Manufacturer and Item #**	**Stage of Use**	**Concentration at Storage**	**Origin**	**Grade (GMP, USP, FDA approved)**	**CoA or package insert on file (yes/no)**	**Lot Qualification Testing Performed (Yes/No)**
Hespan	----------(b)(4)-	(b)(4)	------(b)(4)----	(b)(4)	----------(b)(4)----------	----------(b)(4)----------	(b)(4)
DMSO/	------(b)(4)----	(b)(4)	----------	(b)(4)	(b)(4)	(b)(4)	----------

Material	Manufacturer and Item #	Stage of Use	Concentration at Storage	Origin	Grade (GMP, USP, FDA approved)	CoA or package insert on file (yes/no)	Lot Qualification Testing Performed (Yes/No)
Dextran ----------b)(4)-			--(b)(4)-				-(b)(4)---------- ------
DMSO/ Dextran ----------b)(4)-- ---------	----------b)(4)-	(b)(4)	----------b)(4)-	(b)(4)	(b)(4)	(b)(4)	----------b)(4)---------- ------

*animal origin free

Hespan

CCBB uses a sterile commercial grade and FDA approved Hespan to aid in red blood cell sedimentation and volume depletion. Hespan (----------(b)(4)----------) is accepted for use based upon the review of the Package Insert and labeling on the Hespan container for each lot received. Hespan is supplied as ----------b)(4)----------.

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

DMSO/Dextran

-----(b)(4)----- DMSO and Dextran-40 ----------(b)(4)---------- is used as a cryoprotectant solution for the leukocytes isolated during CBU processing.

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

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

Control of Critical Steps and Intermediates
Samples are taken throughout the manufacturing process to monitor and maintain critical attributes of the CBU. Specifications and acceptance criteria have been developed for the in-process steps listed below which are performed on each HPC-C product, and the results from the analyses help determine whether the CBU proceeds to the next manufacturing step or if it should be disposed of according to standard procedures.

(b)(4)

(b)(4)

Collection - Post-Collection Volume
The ----(b)(4)---- cord blood procedure allows for efficient processing of initial CBU volumes from ----(b)(4)----. The --(b)(4)-- cord blood procedure, which is not part of this license application, can be used for (b)(4) volume CBUs (----------(b)(4)----------). However, at this time, processing is not routinely performed on any cord blood sample where the initial volume is ------(b)(4)------ (cord blood volume alone without anticoagulant). CBUs ------(b)(4)------ are discarded per CCBB-LAB-005.

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

CCBB has chosen (b)(4) as their minimum volume based on the probability that a CBU of a certain volume will contain --(b)(4)-- cells. Only (b)(4) of CBUs with a volume ------ (b)(4) will contain sufficient cells to proceed with processing.

Collection – Storage and Transport
For coolers arriving from local collection sites, the date and time of receipt are recorded on the Shipping Log (CCBB-COL-009 (FRM 1)) to allow for the calculation of time from collection to receipt.

For coolers arriving from remote collection sites, the data logger in the ----------(b)(4)---------- shipper is examined to ensure that the shipper and cord blood stayed within the room temperature range during transport. Data for all shipments are downloaded once per day, and if a temperature is out of range, a deviation is reported. However, if the viability of the CBU after processing still meets acceptance criteria, the unit can continue to be processed.

Processing - Time from Start of Collection to Initiation of Freezing
After collection, the time that collection was started is written on the collection bag. The corresponding expiration date/time is verified upon receipt at the Processing Laboratory and is carried over to the cryopreservation form/manufacturing batch record to ensure that cryopreservation is initiated within 48 hours of this time. If the CBU does not begin the freezing process within 48 hours of collection, the unit will be disposed of per standard procedures. The computer system, -(b)(4)-, also provides a check that this criterion has been met for each HPC-C product. If criteria have not been met, the unit cannot be uploaded to the donor registry.
It has been shown that cord blood maintains viability at room temperature for -(b)(4)-, and thus, the 48-hour cryopreservation deadline is well within this time frame. CCBB has chosen the 48hour window to ensure that the HPC-C products have maximal potency.

If processing cannot be completed within 48 hours, this will result in disposition of the product according to CCBB-LAB-005. Disposition of any nonconforming CBU may include the product being disposed of as biological waste or utilizing the product or its components for research, training, or quality control.

Processing- Evaluation of Freezing Curve
The HPC-C products manufactured in the CCBB are frozen using the ThermoGenesis BioArchive, which contains an internal, programmed controlled rate cooling program. The freezing of a CBU product bag in this BioArchive system occurs immediately after overwrapping the cryobag and placing it into the steel canister. Once the freezing program is complete and the canister has been stored in liquid nitrogen, the freezing graph and storage location will automatically print out. This freezing curve is reviewed

by trained personnel, and any abnormal results are brought to the attention of a supervisor.

Additionally, these freezing curves are reviewed prior to release of the CBU to long-term storage and again prior to transport of the CBU to a transplant center.

On the freezing curve, the post-freeze temperature change between ------(b)(4)------ must occur within -----(b)(4)-----. This post-freeze transition should occur at a rate of ------(b)(4)-----, which would reduce the temperature of the product from ----------(b)(4)----------.

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

Units with a freezing curve that does not meet these parameters are disposed of per standard procedures.

Control of Intermediates
The manufacturing of the HPC-C product does not contain any intermediates that are stored for use in a subsequent step. However, there are steps during the processing of the cord blood where reagents are added to the cord blood. For these steps, analysis has been performed to determine the appropriate parameters for the process of combining the material with the cord blood. Theses parameters are listed in the table below.

Intermediate Specifications
Redact 1 page (b)(4)