MEMORANDUM

BLA 125397
CMC Review of Original Submission

Hematopoietic Progenitor Cells- Cord Blood (HPC-C)
HEMACORD™
National Cord Blood Program (NCBP) of New York Blood Center (NYBC)

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

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EXECUTIVE SUMMARY

Recommendation:

We recommend that the BLA be approved. We recommend that approval be granted only for HPC-C units that will be manufactured after the approval date.

Although the applicant requested licensure of HPC-Cs in inventory since August 2006 using the current automated processing method (referred to as Method 4 in this review), 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-C; proprietary name—HEMACORD) is manufactured by the National Cord Blood Program (NCBP) of the New York Blood Center (NYBC). Manufacturing and product quality standards for HPC-C manufactured at NYBC are consistent with recommendations made in the FDA licensure guidance.

The cord blood is processed by volume reduction and partial red cell and plasma depletion using the Thermogenesis AXP automated system. The final product is in 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 (-196^{o}C). Final product is tested for purity, identity, sterility, and potency.

The HPC-C under this license will have a 48 month (four year) dating period. There is a stability program in place to potentially extend the dating period on -----(b)(4)--- basis.

HPC-Cs are shipped frozen in special shipping containers (Dry-Shippers) designed to maintain a controlled environment and a very low temperature ($\leq$ -150^{o}C). Shipping must occur within --(b)(4)-- and temperature is electronically monitored and recorded for the entire transit time.

(b)(4) alternative thawing and preparation procedures have been validated and directions for thawing will be included with each shipped HPC-C.

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

A pre-licensure inspection was conducted in April 2011, during which the facility was issued a form 483 citation. The major issues cited included: 1) there was not a Quality Control Unit in place to review the lot release information and release the HPC-Cs; and 2) the batch records were deficient. The issues cited on the form 483 during inspection have been addressed in amendments submitted to the BLA.

GENERAL INFORMATION

The New York Blood Center's (NYBC's) National Cord Blood Program (NCBP) facilities are located at 45-01 Vernon Blvd, Long Island City (LIC), NY, 11101. The Field Establishment Identification number (FEI #) for this facility is 2473015. The trade name of the HPC-C product under this BLA is HEMACORD.

In addition to the LIC processing facilities, the NCBP has eight (8) collections sites, five (5) of which are located in the local New York City area, and three (3) of which are located remotely. The Hospital Collections Sites include the following:

- New York Presbyterian Hospital
- Mt. Sinai Hospital
- Montefiore Medical Center/Albert Einstein College of Medicine of Yeshiva University Weiler Hospital
- North Shore Hospital
- Long Island Jewish Medical Center
- Inova Fairfax Hospital, VA
- University Hospitals of Cleveland, OH
- DeKalb Medical Center, Decatur, GA

All manufacturing steps are under the direct control of the NYBC. The collection staff at these sites report to NCBP for all aspects of cord blood collections performed at the site.

Note: Brooklyn Hospital, New York was a collection site included in the original submission. In an amendment submitted September 29, 2011 (amendment 125379-012), the applicant has added DeKalb Medical Center (Decatur, GA) as a collection site and reports that NCBP has ceased cord blood collections at Brooklyn Hospital.

The NCBP uses outside labs for some safety and identity testing as indicated in the table below.

TABLE 1: List of Testing Laboratories

Test	Performed by	Location	Comments
ABO/Rh	Creative Testing Solutions (CTS)	Tempe, AZ	NYS DOH Licensed
Microbiology-organism identification	Beth Israel* Microbiology Laboratory	New York, NY	NYS DOH Licensed
Infectious Disease Markers**	Creative Testing solutions (CTS)	Tempe, AZ	NYS DOH Licensed
Infectious Disease Markers (stored samples-NAT)	Labs, Inc.	Centennial, CO	NYS DOH Licensed
Hemoglobinopathy Testing	Hemoglobinopathy Referral Laboratory: Molecular testing	Oakland, CA	Children's Hospital Oakland Research Institute NYS DOH Licensed

* The Beth Israel Microbiology lab performs species identification when a positive culture is obtained by the NCBP Bacteriology lab.
**Additional selective ID testing (e.g. HBV PCR in stored samples or testing for toxoplasmosis is provided by Focus Laboratory (Focus Diagnostics, Inc., Cypress, CA)

BACKGROUND/HISTORY

The National Cord Blood Program (NCBP) of the New York Blood Center (NYBC) is the manufacturer of the minimally manipulated, unrelated placental/umbilical hematopoietic progenitor cells, HPC-C, under this license application. The sponsor also has an approved investigational new drug (IND) application (IND 6637) with the agency submitted in 1996. The sponsor has also had two pre-BLA meetings (2005 and 2006) with the agency. As of 11/30/2010, NCBP has distributed –(b)(4)-- HPC-C to 3,798 patients.

Since the establishment of the NCBP in 1992, four methods of manufacturing have been used.

'Method 1' was used during the early years of establishment, in 1993 - 1994. Under this method, the whole cord blood unit was frozen in 10% DMSO and stored under liquid nitrogen in conventional Dewars liquid nitrogen freezers.

'Method 2' was employed between August 1994 and April 1998. During this period, the procedure was changed to reduce the volume of the cord blood to a standardized volume of 25 ml prior to cryopreservation.

'Method 3' was initiated with the introduction of the Thermogenesis BioArchive system (a robotic freezer which includes controlled-rate freezer modules) in 1999, which allowed the freezing of cyoprotected 25 ml cord blood units within its storage hold and minimized Transient Warming Events encountered during transfer of frozen cord blood units. A

new two-compartment freezing bag was also introduced as well as the use of the 'overwrap bag'. The overwrap tightly binds together the two compartments of the freezing bag with the in-line segments and reduces the difference of the rates of heat escape (cold invasion) during freezing, which for unprotected segments, makes the rate too fast and decreases the viability of cells.

'Method 4' uses devices that automate the volume reduction process using functionally closed processing and cryoprotection in disposable bag sets (ThermoGenesis AXP^{TM}). NCBP validated and adopted the AXP system for cord blood processing in August 2006.

Method 4 is the method that NCBP proposes for licensure in this BLA application.

FACILITY DESCRIPTION: FLOOR DIAGRAMS

The new Long Island City, (LIC), facility will be used for manufacturing under this BLA. This facility was commissioned on April 10, 2009, with the initiation of manufacturing (Method 4) in July7, 2009. Prior to this period, all manufacturing was done at the New York City, NY, facility.

The total usable building area is approximately 75,000 square feet, with approximately 20,000 square feet allocated for National Cord Blood Program activities. The remainder of the space contains NYBC's primary blood receiving, processing, testing, and distribution facilities, and includes support facilities such as quality assurance, training, warehouse, maintenance, and administrative offices. The facility contains no research laboratories or activities.

A basic floor plan of the Cord Blood Facilities in LIC is included in the submission. These facilities include receiving, processing, testing, freezing and storage spaces, as well as warehouse, data entry, and administrative spaces (not shown). Additional Floor Diagrams, including product, sample, personnel and waste flow diagrams, along with detailed narrative descriptions, and detailed descriptions of adjacencies, are included in the BLA section on Establishment Description.

The NCBP maintains a small Cord Blood Collection Room in each hospital. These rooms are located on the Labor and Delivery floors of each hospital, and are approximately 100 square feet in area, and are sized to allow -(b)(4)-- blood collections to occur ------(b)(4)--------. The collection room environment, cleaning, and waste handling are controlled by the local hospital under local, state and Federal guidelines and accreditation bodies. NCBP Staff monitor storage temperature of cord blood post-collection prior to pickup for shipment to LIC.

The sponsor states that using the current manufacturing Method 4, the LIC facility has the capacity to support the processing of up to 50 cord blood units (CBUs) per day in a single shift and increase storage capacity to more than 80,000 HPC-Cs with expansion capability to more than 200,000 HPC-Cs.

Note: An in depth review of comparability was not performed, since HPC-Cs manufactured in the New York City facility will not be included for licensure.

During inspection, the inspection team observed(b)(4)cord blood units processed during the morning session. The number of cord blood units processed depends on how many are received at a time; units are processed as they are received and this capacity may be reached by the end of the day.

HPC-C DESCRIPTION

The final hematopoietic progenitor cells, cord blood (HPC-C) product consists of a 25ml frozen product cryopreserved in 10% DMSO and 1% Dextran 40 and stored in liquid nitrogen (-196^{o}C).

HPC-Cs are cryopreserved in two-compartment freezing bags. The larger compartment contains 80% (20 ml) of the suspension, and the smaller compartment contains 20% (5 ml). Each HPC-C may be cryopreserved and frozen in 1 to 2, two-compartment bags, depending on the number of the total cells and the hematocrit at the time of collection. The rationale for freezing HPC-C in two-compartment bags was to allow the removal of the small compartment without thawing the larger. According to the applicant, the idea was to accommodate in vitro cell expansion of part of a unit and transplant together with the unexpanded portion.

The HPC-C is placed and maintained inside a protective metal canister. The steel canisters are labeled and enclosed in a protective plastic foam thermal sleeve. They are shipped frozen in special shipping containers (Dry Shipper) which maintain temperature at ≤ -150^{o}C. The temperature is electronically monitored and recorded during the entire transit time.

The UNII codes, NDC code, and names (proprietary and non-proprietary) of the product are listed below.

Proprietary Name: HEMACORD

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

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

Inactive Ingredients:	**UNII Code:**
DEXTRAN 40	K3R6ZDH4DU
DIMETHYL SULFOXIDE	YOW8V9698H

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

Dosage Form: Injectable Suspension

NDC #: 76489-001-01

DONOR ELIGIBILITY

NCBP's established procedure to determine donor eligibility is based on the donor screening and testing requirements defined in 21 CFR Part 1271, Subpart C and the recommendations defined in FDA's Donor Eligibility guidance (August 2007).

Donor Screening

NCBP's donor screening is performed at two stages. After obtaining the preliminary consent, the birth mother is pre-screened for risk factors listed in the Cord Blood Collection section of the review. The complete donor consent and the donor screening which includes review of the relevant medical records, physical examination reports, and donor and family history questionnaire may be completed after the cord blood collection is completed. Donor screening is performed and documented by the program's qualified nurses or collection staff.

Donor screening procedure includes assessment for the following risk factors:

- Required screening- HIV 1/2, HTLV I/II, HBV, HCV, Syphilis, WNV, Sepsis, Vaccinia, TSE (CJD/vCJD), Xenotransplantation

- Additional risk factors assessed (not currently required)-Parasitic blood diseases such as malaria, chagas, and babesiosis.

The donor history questionnaires (referred to as Data Form in the application) used for the screening of birth mothers for relevant communicable disease agent risk factors include all the recommendations in the Donor Eligibility Guidance (August, 2007). However, the following conditions or behaviors were not included in the donor history questionnaires used for donors collected prior to 8/5/2007:

- History of CJD in blood relatives of the infant donor.
- current or former U.S. military member, civilian military employee who resided at U.S. military bases in Northern Europe for 6 months or more cumulatively from 1980-1990, or elsewhere in Europe for 6 months or more cumulatively from 1980-1996.
- Prior diagnosis of WNV or positive test results for WNV.
- Persons or their sexual partners who were born or lived in certain countries in Africa or received blood transfusion in the listed African countries, since 1977.
- Persons who received xenotransplantation products or had intimate contact with a xenotransplantation product recipient.

The above screening questions were added to the data form version 7/30/07 which was implemented on 8/5/2007.

Reviewer Comment: *The donor questionnaires used for units collected on or after 8/5/2007 meet HCT/P donor eligibility requirements for donor screening.*

Donor Testing

Maternal blood specimens for donor testing are obtained at or within 7 days of birth. Testing is performed at CLIA certified laboratories (certification #s provided) using FDA-licensed, approved or cleared tests. The following donor tests are performed:

- *Required test-:* Anti-HIV 1 and 2, HIV-1/HCV NAT, Anti-HTLV I and II, HBsAg, Anti-HBc, Anti-HCV, Syphilis, Anti-CMV

- *Additional tests performed (not currently required)*- WNV NAT, HBV NAT (if Anti-HBc is positive), Anti-T. cruzi, CMV-(b)(4) by PCR (if anti-CMV is positive)

According to 21 CFR 1271.80, donors must be evaluated for possible infusion of crystalloids sufficient to affect the results of communicable disease testing. NCBP implemented this evaluation on 7/7/2011 (SOP CB37.0006.2).

Reviewer Comment: *The donor testing performed for units collected on or after 7/7/2011 meets HCT/P donor testing requirements.*

For units in the existing inventory that have not been tested for HIV/HCV NAT testing, the sponsor uses a frozen maternal blood specimen to complete the testing. The frozen specimen storage time must be less than ---(b)(4)--- to be in compliance with the test kit's manufacturer's instructions. In SOP CB41.0002.3, sponsor specifies that only units that meet all the FDA criteria will be qualified for licensure. Therefore, if the testing is performed not in accordance with the manufacturer's instructions, the unit may only be used under an IND.

Even though it is not required, NCBP tests a sample of cord blood for Anti-HIV 1 and 2, Anti HTLV I and II, HBsAg, Anti-HBc, Anti HCV, Syphilis, Anti-CMV. However, the infectious disease test kits are licensed, approved or cleared for use with peripheral blood specimens and not the cord blood samples. The unit report which lists all the infectious disease tests performed on both the maternal peripheral blood specimen and the cord blood sample includes a statement indicating that the assays used for the infectious disease tests were approved for the maternal blood specimen.

The results of both the maternal and the cord blood infectious disease tests are included in the accompanying records when the cord blood unit is shipped to the transplant center.

Note: Additional information on the infectious disease tests and validation are documented under the 'Lot Release Tests' section of this review.

Donor Eligibility Determination

The donor eligibility is determined by the Director of Donor Services. The following findings exclude the cord unit from release into the search inventory for clinical use:

- Positive test results for Anti-HIV 1 and 2, HIV-1/HCV NAT, Anti HTLV I and II, HBsAg, Anti-HCV
- Pre-natal positive results for anti-HIV 1 and 2, syphilis, HBsAg, anti-HCV
- Mother had xenotransplantation
- History of TSE in mother, her blood relatives or baby's blood relatives

Donors with the following positive test results are deemed ineligible but the cord unit may be released into the search inventory for use under an IND if there is a documented urgent medical need:

- anti-HBc (HBV PCR negative)
- --------(b)(4)------- test for syphilis (confirmatory test negative)
- WNV NAT
- Anti- T. cruzi

NCBP determines the donor to be eligible if the donor screening does not identify any risk factors for communicable diseases agents or diseases and all the test results are negative or non-reactive (except for CMV). CMV results are reported to the transplant physician; however, donor CMV status is not a criterion for donor eligibility. Only cord units from eligible donors are considered qualified for licensure as long as all other requirements have been met.

Regarding plasma dilution, NCBP determines the donor to be ineligible if the birth mother has received more than 2000ml of transfused blood components and/or colloid within 48 hours of maternal donor testing specimen collection. In cases where cord blood units are collected from donors who are determined to be ineligible because of suspected plasma dilution due to transfusion of blood components or infusion of colloid, the sponsor indicates that the products will only be released under an IND, if there is a documented urgent medical need.

Reviewer Comment: *The sponsor's approach for determining the donor as ineligible if there is suspected plasma dilution due to transfusion of blood components and/or colloids is consistent with the regulations 21 CFR 1271.80(d)(2). However, if there is sufficient plasma dilution in the donor prior to obtaining the donor testing specimens, the results of communicable disease testing may be affected. Therefore, to adequately and appropriately reduce the risk of transmission of relevant communicable diseases in such cases, we recommend that when possible, the sponsor performs the donor testing in accordance with 21 CFR 1271.80(b), which allows for the collection of donor testing*

specimens up to 7 days before or after collection of the cord blood. This recommendation was communicated to the sponsor during a teleconference on 7/27/2011. Sponsor decided not to change the procedure since their approach for handling cases of possible plasma dilution in the birth mother was consistent with the regulations.

Effective August 1, 2011, NCBP has implemented a stepwise designation mechanism in their internal database to track the cord unit status throughout the review and release process before units are released into the search inventory. Cord units remain under the quarantine status "Q" until the donor eligibility determination has been made and the quality review has been completed. Cord units that are accepted for release into the search inventory are either flagged with an "L" (if all the criteria for licensure are met) or with "IND". The status of the cord units during the various stages of distribution are also flagged in the system (e.g. reserved, released for transplantation, transplanted).

Reviewer Comment: *Units collected prior to 8/1/2011 will not meet GMP requirements since the quality review will be performed retrospectively after units have been listed in the registry (also see DMPQ review).*

NCBP includes the final donor eligibility statement, summary of records used to make the donor eligibility determination, the listing and interpretation of the infectious disease test results and all other information required under 21 CFR part 1271.55 in the accompanying records when the cord blood unit is shipped to the transplant facility.

Reviewer Comment: *The donor screening, testing and final donor eligibility determination performed by NCBP is in accordance with 21 CFR 1271, Subpart C regulations as well as the recommendations provided in the donor eligibility guidance document.*

CORD BLOOD COLLECTION

NCBP performs the cord blood collection at 8 designated hospitals (5 located in the state of New York, 1 in Virginia, 1 in Georgia, and 1 in Ohio).

NCBP establishes a contract with each hospital that includes use of space and reimbursement of costs borne by the hospitals. This contract does not include any manufacturing arrangements. NCBP staff at each hospital is responsible for obtaining maternal consent, collecting the cord blood units and performing the initial donor qualification screening. Collection staff is trained on all SOPs associated with the collection procedure by NCBP. Initial training and assessment includes a ----------(b)(4)---------- of hands-on training at the New York Presbyterian Hospital (an affiliate of NYBC). Staff must pass an assessment at the end of the training. After initial training, staff are observed -(b)(4)- to ensure proper technique is used. Staff competency is also performed and documented on annual basis.

Reviewer Comment: *The above approach will be acceptable for adding new collection sites in the future.*

Prior to the collection of cord blood, maternal consent is obtained, which is divided into two parts:

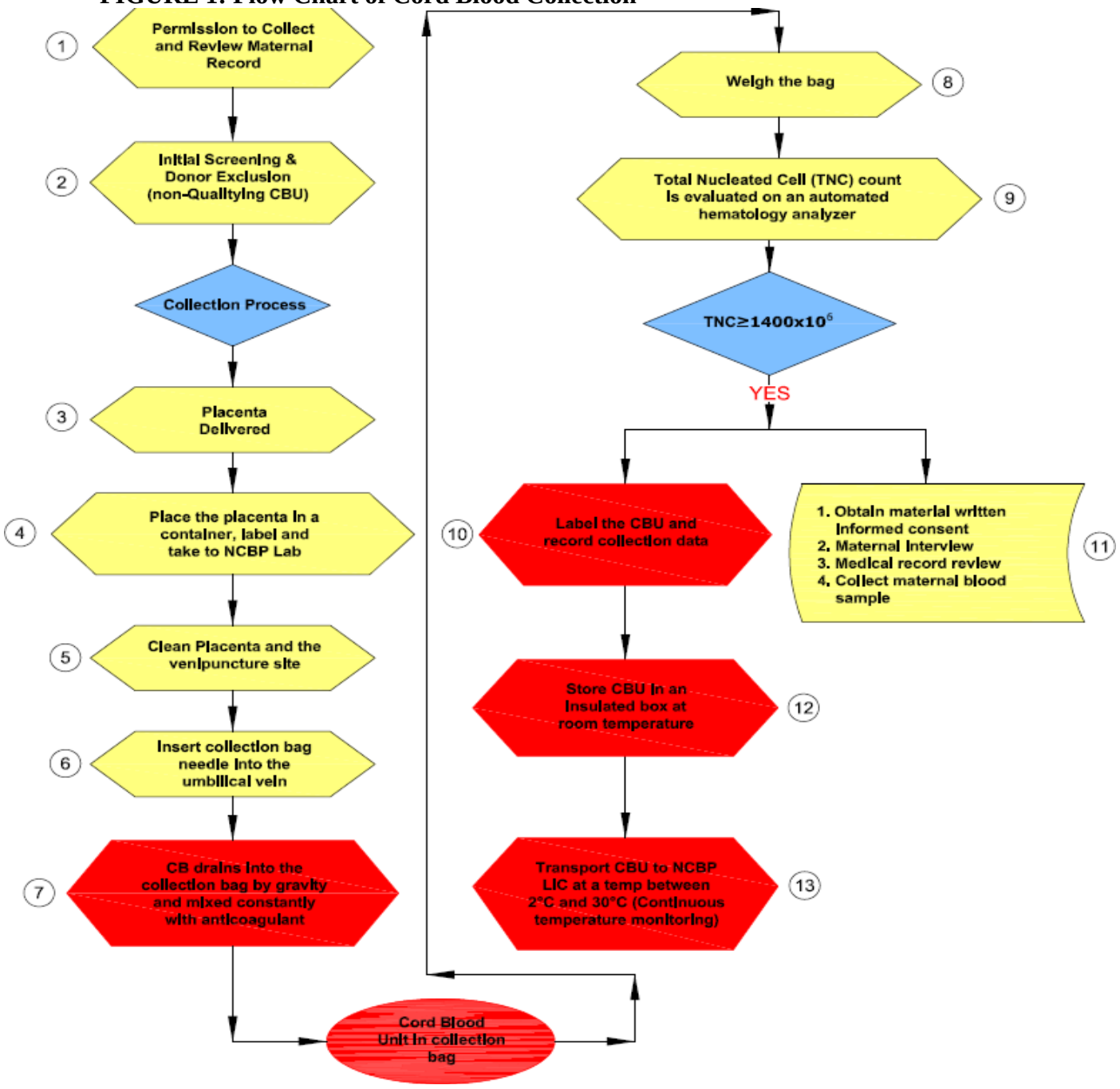
1) Permission to collect and review medical records to pre-screen the mother for risk of infectious diseases. Collection is not attempted if the maternal pre-screening identifies any of the following conditions:
- Prenatal positive test HIV, HBsAg, HCV, HTLV I/II, syphilis
- Sepsis, blood transmissible infection, toxoplasmosis, sexual contact with men who have or are at risk to HIV infection
- Potentially transmissible genetic disease
- Pregnancy involves anonymous egg or sperm donation
- Mother has vCJD or has blood relative with vCJD
- Mother had cancer or leukemia (any time before) or received chemotherapy or immunosuppressive drugs during the pregnancy
- Mother had received xenotransplantation or lived in a household with a person who did.

The following infant conditions disqualify the donor:
- Infant with a genetic disease
- Infants that received an *in-utero* transfusion
- Fetal demise

2) Full written consent which is obtained either before or after the collection of cord blood.

Cord blood collection is performed *ex-utero* following established procedures. The following flow chart summarizes the collection steps:

FIGURE 1: Flow Chart of Cord Blood Collection



Collection Controls

NCBP has established the following controls for the collection procedure:

- At each collection site, cord blood is collected in a dedicated access-controlled area located near the delivery rooms.

- After delivery of the infant, collection staff retrieves and transports the placenta (placed in a covered, labeled container) from the delivery room to the dedicated collection area.
- To minimize risk of contamination: 1) collection is not performed if the placenta or cord is damaged, 2) collection staff wear appropriate gowning and protective equipment, 3) Venipuncture site on the cord is cleaned with antiseptic solutions prior to the insertion of the needle on the collection bag.
- Unit collection is performed ---(b)(4)---- and the staff member collecting the unit is also responsible for labeling the unit and all the associated paperwork.
- Relevant information such as collection date, time, collection bag lot #, expiration date, collecting staff initials and ID number are documented on the collection form by the person collecting the cord blood unit.

Initial Qualification Criteria

The collection staff at each collection site determines if the unit meets the initial qualification criteria [$\geq 1400 \times 10^6$ total nucleated cells (TNC)] by performing an automated cell count. If the cell count is not available, --(b)(4)-- volume is used as the initial qualification criteria. A cell count may not be available because the clinical lab at the collection site does not provide cell count results at the time of collection. The cell count or volume criteria are used at the collection site to determine if the cord blood should be sent for potential processing. Qualified units are assigned a bar coded unique identification number (refer to the Tracking section for more details) prior to the temporary storage and transportation. The cell count performed at the collection site is not used as the acceptance criteria prior to processing of the cord blood unit: the cell count is repeated at the processing laboratory and the cell count performed at NYBC is used to determine acceptability for further processing. A barcode is not assigned to cord blood units that do not meet the initial qualification but these units are sent to the processing laboratory to be discarded or used for research.

Storage and Transportation

Cord blood units are stored temporarily at the collection facility at room temperature and are then transported daily (Monday-Friday) to NCBP laboratory by a dedicated courier service (for hospitals in the New York area) or on daily flights using a dedicated shipping carrier (for hospitals located outside the NY area). Units are shipped at temperature between 2^oC and 30^oC with continuous monitoring while in transit. The shipping of collected cord blood units from the collection sites to the processing facility was validated. Refer to Collection Validation in this section.

Collection Bag and Supplies

Cord blood is collected in sterile, pyrogen free, disposable collection bags containing (b)(4) CPDA-1 anticoagulant ----------(b)(4)----------. If the final weight of the collected unit is ----------(b)(4)----------. Other supplies

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

--*(b)(4)*--
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- ----------(b)(4)----------
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[(b)(4)]

Reviewer comment: *The validation of the collection procedure which includes the use of the -----(b)(4)--------- collection bag and the transport to the processing facility is adequate.*

CORD BLOOD PROCESSING

All processing and storage of HPC-Cs occurs at the NCBP facility located in Long Island City, NY. Processing is performed in three consecutive steps that are completed within ---(b)(4)---- of collection: 1) Accessioning; 2) Volume reduction; 3) Cryopreservation, Freezing, and Storage. Each step is described in a separately numbered and titled SOP and requires generation of computer and hard copy forms and labels.

- Accessioning: entry of cord blood units into computer database

- Volume Reduction of cord blood units: preparation of mononuclear cell enriched fraction using the AXP AutoXpress™ Platform
- Cryopreservation, Freezing and Storage of cord blood units: includes addition of DMSO/Dextran 40 cryoprotectant, controlled freezing to Liquid Nitrogen temperature and storage in BioArchive System.

Records are made concurrently with each step of processing and banking. Personnel of the Processing Lab initial the form records (hard copy) and log-in with their credentials into the computer database, so their name is added to the computer record after each step of the procedure for which they are responsible. All records carry the date and time, as appropriate.

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

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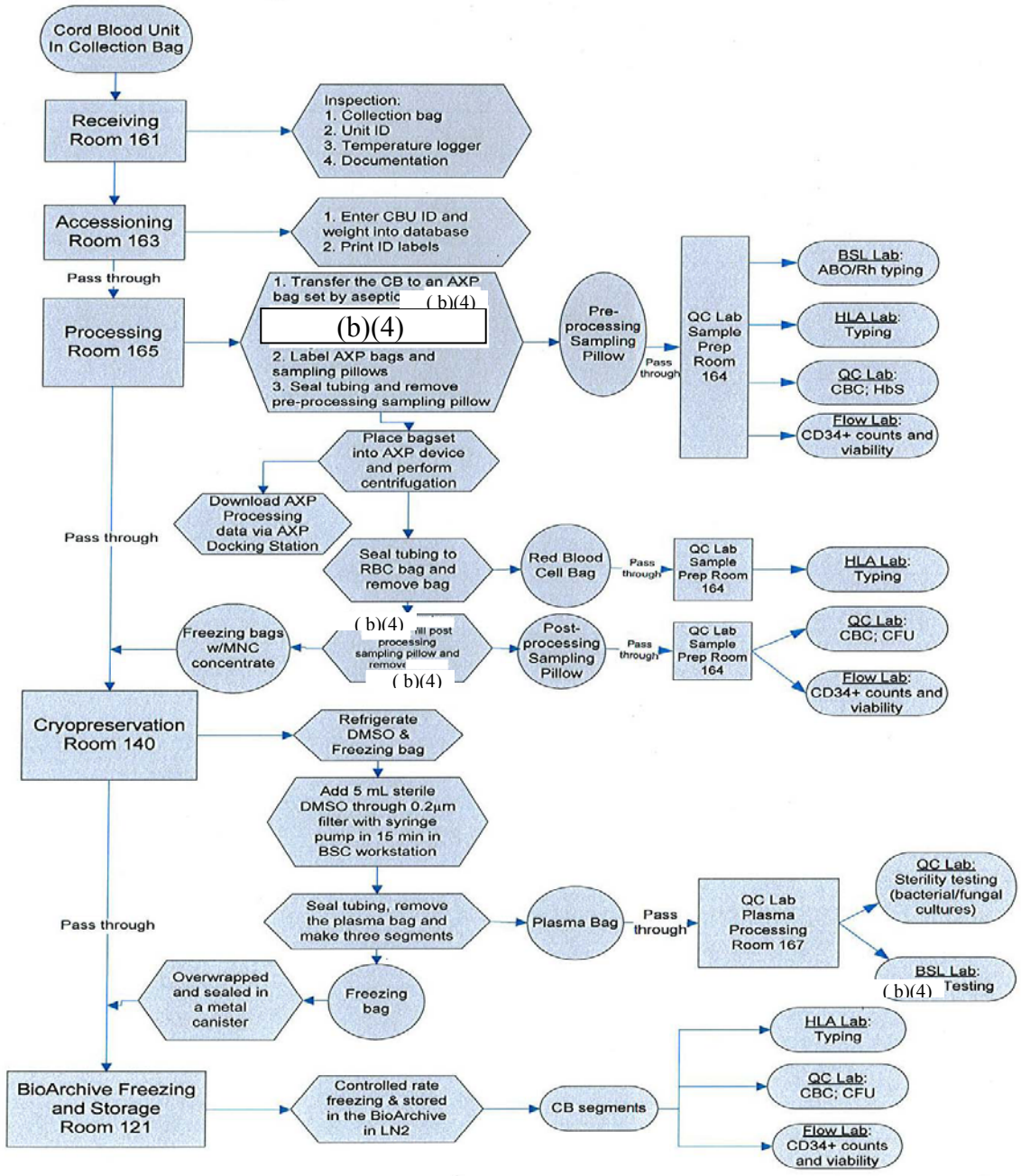
FIGURE 2 : Processing Flow Chart



CORD BLOOD PROCESSING VALIDATION

Protocol NCBP-VAL-10-012P was followed for the process validation study to demonstrate that the cord blood processing procedures at NCBP of New York Blood Center at Long Island City can consistently yield a product that meets its pre-determined specifications, including viability of cord blood cells and product integrity.

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

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

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[(b)(4)]

***Reviewer Comment**: The process validation results are adequate.*

Note: Aseptic process validation is reviewed separately later in this document.

SHIPPING OF HPC-C

HPC-Cs are shipped in liquid nitrogen filled dry-shippers (also called cryoshippers) to transplant center locations worldwide. Shipping is accomplished using either a courier service or express delivery service with defined delivery times. The applicant reports that as of August 31, 2010, a total of (b)(4) HPC-C from NCBP have been shipped to 38 countries for 3,693 patients.

The dry-shippers are used to ship the HPC-C to the end-user. These dry-shippers are vacuum-insulated metal containers with liquid nitrogen dispersed in an absorbent material that allows for steady flow of cold vapor nitrogen into the cryostorage area (HPC-C holding area). In an upright position, they are designed to maintain cryogenic temperatures (< -150^{o}C) for a period of –(b)(4)- (maximum, for static hold only) depending on liquid nitrogen load. Sponsor states that the data-loggers ----------
-------(b)(4)---------- are calibrated for use to a temperature down to (b)(4). The sponsor applies the ----------(b)(4)----------
specification for shipping HPC-Cs, which specify that ----------
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----------(b)(4)----------

The sponsor has determined that (b)(4) duration is sufficient to ship the CB product to any of NCBP's client Transplant Centers worldwide and be in compliance with the SOPs and

standards. Hence, in the shipping validation, NCBP qualifies dry-shippers as able to maintain the temperature of -150°C or colder for ----(b)(4)------.
Manufacturer information on the dry-shippers and temperature loggers used by NCBP is listed below:

Dry-shipper ----------(b)(4)----------
Temperature Monitors ---------(b)(4)----------

SHIPPING VALIDATION

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

[(b)(4)]

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

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Reviewer Comment: *The shipping validation protocol is adequately executed and demonstrated that the NCBP procedures for shipping HPC-Cs to transplant centers result in the receipt of units with intact container closures at the prescribed temperature (≤-150°C) within the (b)(4) time frame. All the dry-shipper weights met the established criteria of --(b)(4)--.*

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

Reviewer Comment: *The sponsor has provided shipping validation information based on their protocol and shipping to different destinations. Although, the sponsor has not analyzed the product at the end of the shipment, there is evidence to support that the set temperature of ≤-150°C maintains the HPC-C viability. The sponsor follows the -------(b)(4)---------- for shipping HPC-Cs. These standards specify that the dry shipper is validated to maintain ≤-150°C for at least --(b)(4)--. These conditions are sufficient if the temperature is maintained at ≤-150°C. There is also information in the literature which supports product viability when maintained at the set temperature.*

THAWING AND CRYOPROTECTANT REMOVAL: VALIDATION SUMMARY

The sponsor states in the BLA submission that a thawing protocol is attached while shipping a HPC-C unit in a cryoshipper to the clinical site. These instructions will also be included at the end of the prescribing information in "Instructions for Preparation for Infusion."

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[(b)(4)]

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Expiration and Holding Conditions for Reconstituted HPC-C

Based on the data provided, the reconstituted (thawed and diluted without washing) HPC-C expires 4 hours either at room temperature or 4°C.

Expiration and Holding Conditions for Washed HPC-C

The sponsor has also provided information that demonstrates that washed HPC-C expire after 24 hours from the date and time of thaw at 4°C.

Reviewer's Comment: *These results demonstrate that the NYBC thawing procedure is considered validated. The procedure can be used either as thawing and reconstitution only, or with the additional step of removing the DMSO-containing supernatant. The data*

presented supports the stability of the reconstituted HPC-C for 4 hours at room temperature or at 4^{o} C, and that of the washed HPC-C product for 24 hours at 4^{o} C.

Note: The HPC-C are cryopreserved in 1% Dextran 40 with DMSO. In the thaw- dilute method, the product is diluted to 170 mL in 5% Dextran 40 with 2.5% Human Serum Albumin (HSA). ----------(b)(4)----------.

The Advisory Committee addressed the issue of infusion reactions likely related to the high concentration of Dextran 40 and asked whether the concentration of Dextran 40 after washing could be lowered. No specific recommendations were made.

The review team considered what type of data could be generated to address this issue. One option would be to have NYBC study the impact of lower concentrations of Dextran 40 on cell viability, potency, and stability. However, the review team felt these in vitro studies alone would not address whether a reduction in Dextran 40 results in a clinical reduction in infusion reactions. In addition, although NYBC could do the in vitro study portion, and potentially revise their instructions for preparation, it is the transplant centers' decision how to prepare HPC-C for infusion, conduct the infusion, and perform and report on patient monitoring.

A second option would be to work with the transplant community and other interested government agencies such as HRSA and NIH to develop a study that aimed to correlate HPC-C thawing procedures and infusion reactions to develop a plan to mitigate the risk for infusion reactions. A study designed and conducted by a group of stakeholders could yield data relevant to all potential BLAs for HPC-C. The review team favors this second option and we will explore options to facilitate the execution of this kind of collaborative study.

EMERGENCY PRODUCT RECOVERY

These "Instructions for Preparation for Infusion" section at the end of the prescribing label will provide information on emergency product recovery. HPC-C product bags are very fragile. Therefore, the sponsor has provided a detailed protocol for product recovery in case of a container failure. To prevent accidental fracture, the bags must be handled with extreme caution when removing them from the protective metal cassettes, during inspection and during the thawing process. It is recommended that the thawing process be performed in a controlled laboratory environment which provides appropriate equipment and supplies for post-thaw sampling and/or bag rescue, as well as dedicated space and personnel for product preparation.

To mitigate the extreme temperature change from storage at -196°C (Liquid Nitrogen phase) to thawing at 37^{o}C and possible sudden vaporization of liquid nitrogen, transfer the bag with the product from the liquid phase of nitrogen to the vapor phase for a period of time (a few minutes) before removal for thawing. To prevent an accidental drop onto

the floor, HPC-C bags must be handled over a flat surface, such as a table. It is recommended that all HPC-C products be placed in individual sterile zipper-locked bags prior to thawing to facilitate salvage of the product and reduce contamination in case of an unanticipated problem. In the SOPPs, the sponsor has instructed the transplant centers that if the HPC-C bag is obviously fractured upon removal from cold storage, or if it fractures during the thawing process, they should notify the NYBC-NCBP Processing Laboratory as soon as possible. The sponsor has also suggested to notifying the transplant physician and the laboratory director immediately. It is the transplant physician's (or designee's) responsibility to determine whether the HPC-C product will be used or discarded and whether additional HPC-C product(s) are to be requested for infusion. If the transplant physician (or designee) determines that the product in the ruptured bag should be used, the HPC-C product may be recovered per following steps:

1. Place the ruptured bag into the sterile zipper-locked plastic bag to prevent further loss and/or contamination of the product during the thawing process.
2. Thaw the product according to the instructions provided.
3. Small leaks or tears of the ruptured bag can be blocked off with hemostat clips.
4. Withdraw the thawed product from the freezing bag and any product from the zipper-locked bag into one or more 60 mL syringe(s) with sterile tubing attached.
5. The product may be transferred via sterile syringe inside a biological safety cabinet into a new container. This new bag could be either the sterile Transplant bag that is provided with the product or a bag of a stocked salvage kit that should be readily available in the thawing laboratory for use in these situations.
6. Save an aliquot of the product and send for gram stain and bacterial and fungal cultures.
7. Dilute (reconstitute) the thawed product and remove the cryo-protectant according to the procedure described above or administer the diluted product to the patient as per transplant physician's instructions.
8. It would be the transplant physician's (or designee's) responsibility to determine whether to treat the patient with broad-spectrum antibiotic coverage and the necessity for an infectious disease consultation.
9. If possible, please save the ruptured bag (with or without HPC-C) and place it into a biohazard bag.
10. Notify NCBP staff. NCBP staff will notify the manufacturer and provide information for returning the bag to the manufacturer for evaluation.

Reviewer Comment*: As per guidance, the sponsor has described the emergency product recovery protocol in SOP CB38.0006.1. This SOP and the attached protocol provide instructions and details to recover the HPC-C product in case of an emergency of bag breakage or leakage.*

STABILITY PROGRAM FOR EXPIRATION DATING

The applicant has a stability program in place to assess the stability of the Frozen HPC-C in support of the storage conditions and to monitor and advance expiration dating. The

protocol is described in document NCBP-STB-10-001P, titled: *Stability Testing Protocol of Cord Blood Units (HPC-C) Processed Using Four Distinct, Successive Cord Blood Manufacturing Processes*. A report on the initial stability testing executed in 2010 is contained in document NCBP-STB-10-001R1, titled *Stability Testing Report of Cord Blood Units (HPC-C) Processed Using Four Distinct, Successive Cord Blood Manufacturing Processes-2010,* which summarizes 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-Cs --(b)(4)---. Because of the different periods of storage of HPC-Cs produced by each manufacturing method (four manufacturing methods used sequentially between 1993 and 2006), this protocol assesses the stability of all four manufacturing methods. NYBC proposed that the results will be used to extend the shelf life --(b)(4)- and increase the expiration date of HPC-Cs processed and stored by each method. Table 16 shows the number of HPC-Cs available in search inventory as of October 6, 2010.

[(b)(4)]

[(b)(4)]

Description of Stability Protocol

(NCBP-STB-10-001P)

At the start of the study, (b)(4) HPC-Cs will be --(b)(4)--- selected for testing from those produced in the first year of implementation of each manufacturing method. During each subsequent year, (b)(4) HPC-Cs will be –(b)(4)--- taken from the same time/method cohorts for testing. The HPC-Cs will be thawed ----------(b)(4)----------. Their containers will be examined for overall integrity (label, closures, tubing, tubing seals, and the contents tested for indices of sterility, identity and potency (Table 18). Data collected in the study will be evaluated against the acceptance criteria listed in Table 19.

TABLE 2: Stability Testing of Frozen/Thawed HPC-C

Test	Purpose	Stability-Indicating	Testing SOP
Visual Inspection after thawing	Determine Integrity of container and closures and Identity Label	Integrity, Identity	OPP5
Total nucleated cell (TNC) count	Measuring TNC content	Potency	OPE6
Viable CD34+ cell content	Measuring CD34+ cell number and viability	Potency	27.0090.3
Colony-Forming Units (CFU)	Counting colonies of functional progenitor cells	Potency	OP SP2
Microbiology	Detection of microbial contamination	Integrity, Purity, Safety	OPE5

TABLE 3: Acceptance Criteria for Stability Testing

Current Test	Acceptance Criteria	Criteria Apply to Manufacture Method			
		1	2	3	4
Visual Inspection	(b)(4)	(b)(4)		(b)(4)	Yes
TNC Count					Yes
					Yes
					Yes
CD34+ Cell Viability*					Yes
CFU Assay					Yes
Sterility					Yes

*Due to the testing requirements, methods and technology available at the time of freezing for products processed under methods ----------(b)(4)----------.

Pre-specified Criteria

The acceptance criteria used in the stability studies are shown in Table 19.

Execution of Protocol

A report on the initial stability testing executed in October 2010 is contained in document NCBP-STB-10-001R1, titled *Stability Testing Report of Cord Blood Units (HPC-C) Processed Using Four Distinct, Successive Cord Blood Manufacturing Processes-2010.* This report summarizes the stability testing results in support of the current storage conditions.

For the initial testing, (b)(4) HPC-Cs were --(b)(4)--- selected for testing from those produced in the first year of implementation of each manufacturing method. The HPC-Cs were ----------(b)(4)---------- only as per SOP OPP5. The tests performed and SOPs followed are outlined in Table 18.

[(b)(4)]

Integrity of containers and closures: The containers and closures were checked for integrity on each HPC-C subject to the stability study. There were no fractured containers, broken closures, leaks nor freezing bag labels missing, unable to scan or unreadable.

Sterility: All sterility tests results were negative.

Results for potency (TNC, viable, CD34+ cells, and CFU) are shown in Table 20 above. There were no deviations noted during the execution of the protocol.

Data Evaluation and Conclusion

The stability test results obtained in 2010 were summarized and analyzed by the sponsor. The sponsor concluded that there has been no detectable loss of stability in any of the HPC-Cs analyzed, for the criteria investigated. For the manufacturing method 4 under consideration for licensure, the expiration date is set at 4 years based on the 2010 stability studies.

Supportive Data: The applicant presents supportive data from transplanted HPC-Cs to support stability.

The applicant has evaluated clinical outcomes data on patients that received HPC-Cs frozen for over 8 years in comparison to those transplanted with recently frozen HPC-Cs, and reports that no differences in patient and treatment characteristics were found. Results of this analysis are also summarized in Appendix 2 included in the BLA application.

Since the implementation of the current manufacturing method (method 4), segments from manufactured HPC-Cs are thawed and the cells analyzed for CD34+, CD45+ cells, viability and CFU, prior to shipping. In addition, the sponsor evaluates the integrity of the containers and readability of the labels before shipping. The supportive data from transplanted HPC-C prepared by the current manufacturing is included as Appendix 3 to the BLA.

TABLE 4: Proposed Expiration Dates

Period	Method	Volume Reduction	DMSO Source	Overwrap Bag	Freezing and LN Storage	*Current Shelf-life (years)
1993 - 1995	1	No	(b)(4)	(b)(4)	Standard Dewar (LN, (b)(4)	(b)(4)
1995 - 1999	2	Yes Manual			Standard Dewar (LN, (b)(4)	
05/1999 - 08/2006	3	Yes Manual		Yes	BioArchive™ (LN, (b)(4)	
08/2006- on	4	Yes AutoXpress	50%	Yes	BioArchive™ (LN, (b)(4)	

*Last evaluated and confirmed in 2010.

Reviewer Comment*: The stability program described and the results of the initial studies are acceptable. The expiry of HPC-Cs prepared by Method 4 is established as 4 years; this is acceptable. The HPC-Cs used to support this expiry were from the first year of use of Method 4, i.e. 2006; thus the HPC-Cs were 4 years old at the time of use in the stability studies i.e. 2006. The stability data on HPC-Cs manufactured by previous methods also provides supportive data about the stability of HPC-Cs from Method 4*

manufacturing, based on similar containers and storage conditions used. Although units processed in 2006 were not GMP compliant, the data are of sufficient quality and robustness to support a dating period of four years.

LOT RELEASE TESTING

IN-PROCESS CRITERIA FOR PROCESSING:

The collected cord blood has to meet certain criteria to be processed. An initial TNC count is performed at the collection site. If cell count results are not available, the volume of the collected cord blood unit is used as criterion. The in-process criteria is listed in the Table 22 below:

[(b)(4)]

Listed below in Table 23 is a summary of the lot release tests that are perfomed on each cord blood unit, the acceptance criteria, and test methods used. Infectious disease testing is performed on a maternal blood sample, hemoglobin analysis and ABO/Rh typing are done using ----(b)(4)------- cord blood samples, ----------(b)(4)----------.

TABLE 5: NCBP Lot Release Acceptance Criteria for HPC-C

Product Characteristics	**Testing/Inspecting**	**Results on HPC-C ----------(b)(4)-------**	**Test Method**
Safety	Infectious disease - 21CFR 1271.45 thru 1271.90	On maternal blood sample within 7 days of birth. 21CFR1271.80(a)(b) All tests negative, except non-treponemal test for syphilis when confirmatory test is negative. CMV results are recorded	----------(b)(4)----------
	Sterility – Bacterial/fungal cultures	No growth	----------(b)(4)----------
	Hemoglobin	No homozygous hemoglobinopathy	----------(b)(4)----------

Product Characteristics	Testing/Inspecting	Results on HPC-C -------(b)(4)-------	Test Method
Integrity	Container, closures, seals	Intact	------(b)(4)----- -----(b)(4)------
Purity and Potency	Total nucleated cells (TNC)	> 5.0 x 10^8 TNC/unit HPC-C	----------(b)(4)---------- ------
	Viability of CD45+ cells	-(b)(4)-	----------(b)(4)---------- ----------
	Viable CD34+ cell count	≥ 1.25 x 10^6 / unit HPC-C	----------(b)(4)---------- ----------
	Colony Forming Unit (CFU)	Growth	----------(b)(4)---------- ----------
Identity	HLA typing: Cord Blood and HPC-C segment (Confirmatory HLA typing Required*) Maternal HLA Typing	Test Report	----------(b)(4)---------- ---------- ----------(b)(4)---------- ----------
	ABO and Rh	Test Report	----------(b)(4)---------- ------
	Steel Canister and CB Bag ID labels	Labels must match	-------(b)(4)-----

*Prior to release for transplantation

SAFETY TESTING

1. CORD BLOOD DONOR INFECTIOUS DISEASE TESTING

Infectious disease testing will be performed by Creative Testing Solutions (CTS), usually within –(b)(4)-- after receiving shipment. All samples are tested individually, using ----------(b)(4)----------. NCBP submitted SOPs that sufficiently describe the handling, labeling, shipping and data recording of the maternal blood samples tested for infectious disease.

Infectious disease testing description:

Samples from the mother's blood are tested for infectious disease markers (IDMs) using FDA licensed/approved methods and by an FDA-inspected and CLIA (Clinical Laboratory Improvement Amendments) accredited laboratory (CTS). Even though not required by FDA regulations, a sample of cord blood is also tested for IDMs.

TABLE 6: Infectious Disease Testing

Test	Assay name	Manufacturer	License #
Hepatitis B surface antigen	-----(b)(4)----------	----------(b)(4)-------	(b)(4)
------(b)(4)----------	-----(b)(4)----------	----------(b)(4)-------	(b)(4)
Antibody to Hepatitis B core antigen	-----(b)(4)----------	----------(b)(4)-------	(b)(4)
--------(b)(4)----------	-----(b)(4)----------	---(b)(4)-----	(b)(4)
Antibody to Hepatitis C	-----(b)(4)----------	----------(b)(4)----------	(b)(4)
---------(b)(4)----------	-----(b)(4)----------	----------(b)(4)-------	(b)(4)
Hepatitis C, Nucleic Acid Testing	-----(b)(4)----------	------(b)(4)------	(b)(4)
Antibody to HIV-1/HIV-2 --(b)(4)--	-----(b)(4)----------	------(b)(4)------	(b)(4)
----------(b)(4)----------	-----(b)(4)----------	------(b)(4)----------	(b)(4)
----------(b)(4)----------	-----(b)(4)-------	---(b)(4)---	(b)(4)
HIV Nucleic Acid Testing	-----(b)(4)----------	---(b)(4)---	(b)(4)
Antibody to HTLV-1/II	-----(b)(4)----------	----------(b)(4)-------	(b)(4)
----------(b)(4)----------	-----(b)(4)----------	----------(b)(4)-------	N/A - Not Available

Test	Assay name	Manufacturer	License #
West Nile Virus Nucleic Acid Testing	-----(b)(4)----------	-----(b)(4)-----	(b)(4)
----------(b)(4)----------	-----(b)(4)----------	----------(b)(4)----------	(b)(4)
Antibody to Syphilis	-----(b)(4)----------	-----(b)(4)-------	N/A
Antibody to Syphilis	-----(b)(4)----------	-----(b)(4)-----	N/A
Antibody to CMV	-----(b)(4)-----	-----(b)(4)-----	(b)(4)

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

Reviewer Comment*: They perform all the required donor infectious disease testing using FDA licensed or FDA approved (Syphilis) tests.*

Infectious disease testing interpretation:

Reactive infectious disease tests are repeated in --(b)(4)--- using the same screening assay and if results confirm reactivity ("repeated reactive"), a confirmatory test is used. This is in accordance with the test kit manufacturer's algorithm and instructions for initial positive test results. Results of confirmatory tests from samples positive for an infectious disease, are received by fax by the QC lab supervisor, reviewed, and entered into the database manually.

Infectious disease testing validation

CTS validation data consists of staff proficiency test results from assays they performed on commercially available proficiency panels. These tests were performed by multiple operators, three times over a period of a year (2010). Their test plan was intended to show that the testing was accurate and robust.

Reviewer Comments: *The FDA approved or cleared infectious disease tests provide a qualitative result. The consistent identification of both positive and negative test samples is an indication of an accurate and robust test. The validation data supports the use of CTS for infectious disease testing.*

2. HEMOGLOBIN TESTING FOR HOMOZYGOUS HEMOGLOBINOPATHY

The NCBP cord blood units are tested by NYBC personnel for the presence of hemoglobinopathies using the ----------(b)(4)---------- the VARIANT Sickle Cell Short Program. ----------(b)(4)----------and Sickle Cell Short Program are 510(k) (K924813) approved for in-vitro diagnostic use as a qualitative screen for the presence of hemoglobins F, A (normal), S, D, C and E in neonatal blood collected on filter paper. NYBC has previously applied to the Board of Health of New York State to request approval to use the VARIANT system for the analysis of cord blood. Based on validation

data present in this BLA, the VARIANT system was approved for cord blood hemoglobin analysis by the Board of Health of New York State.

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

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

Cord blood samples that contain ----------(b)(4)---------- Hb are sent to the reference laboratory at Children's Hospital, Oakland Research Institute in CA for molecular alpha-thalassemia testing. In addition, if a cord blood unit has a ----------(b)(4)---------- or there is a family history of hemoglobinopathy, a ----------(b)(4)----------. All "Trait" (heterozygous) or homozygous samples are retested to confirm the previous result. Hemoglobinopathy test results are reviewed prior to CB unit release to searchable inventory. All confirmed HPC-Cs that are homozygous for abnormal hemoglobins are permanently deferred.

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

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3. STERILITY

The sponsor of BLA 125397 has proposed to use ----------(b)(4)---------- for testing the sterility of their processed cord blood final product (HPC-C).

The test sample is ----------(b)(4)----------. This sample was proposed because of limited volume of the final HPC-C and the need to conserve the HPC-C cells.

The sponsor originally proposed an incubation period of (b)(4) days. The validation data on slow growing organisms did not support that this method can detect growth in (b)(4) days, thus FDA proposed extending the incubation period to (b)(4).

As of November 4th, 2011, the sponsor has agreed to the recommended(b)(4)day incubation period and revised the respective SOP CB40.0006 accordingly.

Description of the --------(b)(4)----

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

12 pages redacted due to (b)(4)

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

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

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

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

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

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

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

IDENTITY TESTING

Identity testing will include ABO and Rh typing, and initial and confirmatory HLA typing.

1. HLA TYPING

All HPC-C products and the maternal samples are typed for Human Leukocyte Antigens (HLA) by DNA based methodologies at the NYBC HLA laboratory, located in Long Island City, New York. The Laboratory is certified by CLIA (Clinical Laboratory

3 pages redacted due to (b)(4)

2. BLOOD GROUP AND RH TESTING

ABO and Rh typing are performed on all CBUs and maternal samples by Creative Testing Solutions (CTS). The NCBP and CTS both assign identity numbers to the test samples and their equivalence is maintained in both NCBP and CTS databases.

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

The maternal blood sample is ABO/Rh typed on the ----------(b)(4)----------. If type cannot be determined on this machine the samples are subsequently tested in the ----------(b)(4)----------.

Maternal and cord blood samples that do not type using the ----------(b)(4)---------- will be further tested with manual tests.

ABO/Rh Validation studies:

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

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

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

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

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

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

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

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

Reviewer Comment: *The validation information supports the use of CTS for ABO/Rh typing.*

POTENCY TESTS

Total Nucleated Cells (TNC) is the --(b)(4)-- potency test, but viable CD34+ cell counts, CD45+ cell counts (Nucleated cells), viability, and Colony Forming Units (CFU) are also used as complementary data for the evaluation of the quality and potency of a HPC-C product.

1. TOTAL NUCLEATED CELL COUNT (TNC)

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

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

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

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

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

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1 page redacted due to (b)(4)

[(b)(4)]

Reviewer Comment:
The validation accuracy, precision, linearity, and robustness data supports the use of the ----(b)(4)---------- for Total Nucleated Cell Counting.

2. COLONY FORMING UNIT (CFU) ASSAY

Health Resources and Services Administration (HRSA) requires CFU reactivity for its "National (High Quality) CB unit Inventory" (NCBI) to help support the quality assessment of a CB unit. NCBP participates in the NCBI study and thus must perform the CFU assay.

The minimal acceptance Criteria for the "National (High Quality) CB unit Inventory" (NCBI) is colony growth in the CFU assay. The NYBC goes beyond this minimal requirement and tries to determine the quantitative variability of the CFU assay.

Note: Failure or invalidation of a CFU assay will prevent the CB unit from being included in the NCBI inventory but the CB unit could still be "licensed" depending on its CD34+ and TNC counts.

7 pages redacted due to (b)(4)

[(b)(4)]

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

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

Additional Information on Flow Cytometry, Instrument Quality Controls

Section 4.4 of the BLA has a description of the NYBC flow cytometry laboratory (FCL). The FCL operates as a service, reference laboratory and is licensed by the New York State (NYS) Department of Health to perform cellular immunology testing.

Training and Competency

The FCL maintains training records for all technical and supervisory staff. Competency is assessed annually. The FCL performs ----------(b)(4)---------- testing ---(b)(4)-- a year and special staff testing exercises to evaluate technologist performance throughout the year.

Instrument quality control and maintenance is performed according to the current version of NYBC SOP 27.0015, "Cytometer Instrument Quality Control", NYBC SOP 27.0008, "Flow Cytometer Fluidics Preventive Maintenance Procedure" and NYBC SOP 27.0094, "Flow Cytometer Instrument Set-Up for CD34 enumeration and viability assays". CD45+ and CD34+ cell counts and viability are evaluated according to the NYBC SOP 0090 - "Enumeration and Viability Determination of CD34 and CD45 Positive Stem Cells by Flow Cytometry". Commercial ---(b)(4)---- controls are ----(b)(4)---- before routine samples are measured. Results are valid only if the controls fall into accepted range values.
Acceptance Criteria – ----(b)(4)---- for all parameters analyzed

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

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

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

----------*(b)(4)*----------
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New Flow Cytometer Instrument Validation
Section 4.7 of the BLA contains information on new instrument validation and comparability studies
Method - Installation of new flow cytometer in the Flow Cytometer Laboratory requires installation qualification according to the procedures outlined in SOP 27.0011.A (New or Relocated Instrument Validation). In this protocol, the manufacturer performs installation qualification with the assistance of the NYBC FCL staff and provides training as indicated. The laboratory staff then qualifies the instrument by performing comparative studies according to SOP 27.0012.3 (Comparative Study – Flow Cytometry Workstations). SOP 27.0011.A and comparative study results are on file in the NYBC FCL. ------(b)(4)---------- samples are analyzed using SOP 27.0090 on the new instrument

and on a previously qualified instrument. Results are compared using linear regression analysis and t-test.

***Review Comment**: In a telecon with the sponsor on 7/13/2011, the sponsor agreed that accuracy, precision, and linearity tests will be used to qualify new instruments.*
Submission 10 contains the new SOP: Flow Cytometry Validation SOP 27.0011 (Draft) – This document was created to establish a standard operating procedure for the validation of a new or relocated Flow Cytometer.
In addition to QC of the instrument linearity and fluorescence sensitivity, the candidate instrument will be assessed by analyzing ----------(b)(4)---------- samples on an established instrument and the candidate instrument will be performed.
- Linearity will be accepted when R^2 for each parameter--(b)(4)---.
- Accuracy is acceptable if all replicates of control cells fall within manufacturer's range. Lower limit of detection for each assay is established when the respective - - - Low Level control fall within the manufacturer's range.
- Precision for CD34 is acceptable if CV--(b)(4)-- for each sample type, unless otherwise specified by the manufacturer's package insert.
- Correlation between instruments is acceptable when R^2 for each parameter--(b)(4)-- or no statistical difference is detected through analysis of variance.
This is acceptable.

Overall Reviewer Assessment for Flow Cytometry
The sponsor has 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 adequate to ensure consistent performance of this assay as part of manufacturing. The flow cytometry laboratory has adequate procedures for instrument quality control, instrument validation, installation of new flow cytometers, and training of staff.

FINAL SIGN OFF AND HPC-C RELEASE

As of August 2011, NYBC has a Quality Unit in place that performs final review and sign-off of all processing and testing information on a HPC-C prior to release into search inventory. Before that, there was not an independent quality unit in place that was responsible for releasing product lots and the Director and/or Medical Director were responsible for final overall review of patient CB unit information. NYBC was cited for this practice during the pre-licensure inspection and the creation of a quality unit in August 2011 adequately addressed this issue. Final review includes HLA match grade, CB unit's HLA confirmatory typing, patient's confirmatory typing, possible ambiguities in HLA typing on day of processing of selected CB unit, final review of all infectious

disease testing, pre- and post processing complete blood counts and differential, processing notes, patient's informed consent, and IRB/Ethics committee approval.

RETENTION SAMPLES

Information on storage aliquots is described under section 1.2.4 of the Methods of Manufacturing document (document 4.1.5. page 6/14). Sponsor reports that aliquots of plasma, viable cells and DNA from the cord blood unit, and maternal blood samples are separated and preserved for future testing. However, there is no further information on the management of these samples.

In response to information requested during the pre-licensure inspection, sponsor submitted the information summarized below in an information amendment submitted to the BLA on May 27, 2011:

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

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

Sponsor indicates that the retained samples are stored indefinitely.

Note: After discussion with the Agency about the regulatory requirements for a retention sample of the final product, in an October 12, 2011 submission, the sponsor proposed to retain the ---(b)(4)---- segment to meet the retention sample requirement. ----------
---

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

Reviewer Comment*: The segment is the closest sample representative to the final product. Hence, retention of this sample complements the other samples and the samples retained are adequate.*

REAGENTS USED IN MANUFACTURE

The cryoprotectant DMSO/Dextran 40 -----(b)(4)---------- from ----------(b)(4)---------- , is the only reagent that is added to the processed cord blood, HPC-C. Each vial of the sterile 50% DMSO ---------(b)(4)------, contains (b)(4) ml of the solution, and kept ----(b)(4)-----. Per COA, this reagent is ----------(b)(4)----------.

TABLE 7: Reagents Used in Manufacturing

Reagent Name	Final Conc	Vendor	Source	Grade	COA
DMSO/Dextran 40 ------(b)(4)-----	10% DMSO 1% Dextran	----------(b)(4)----------	---(b)(4)----	(b)(4) grade	Yes

Note: A certificate of analysis was submitted upon request during pre-approval inspection and also submitted in the amendment submission on May 18, 2011. New shipments of cryoprotectant are sampled for –(b)(4)-- testing; ----------(b)(4)---------- are tested (information gathered during pre-licensure inspection).

An identity test of the cryoprotectant by ----------(b)(4)---------- was also submitted with the May 18, 2011 submission. Both documents are adequate. NYBCreports that prior to June 18, 2007 when the change to ----------(b)(4)----------.

The DMSO is stored -------(b)(4)---------- (information gathered during pre-licensure inspection).

Reviewer Comment*: The information submitted on the reagents is adequate.*

LABELING AND TRACKING

<u>In-Process Labeling</u>

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

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

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

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

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

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

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

Container and Package Labels

Container:
The product container for Hemacord is cryobag, which is the freezing bag of the AXP Processing Bag Set. Due to the small size of the bag, the affixed label does not include all of the information required for a full container label, and is thus a partial label.

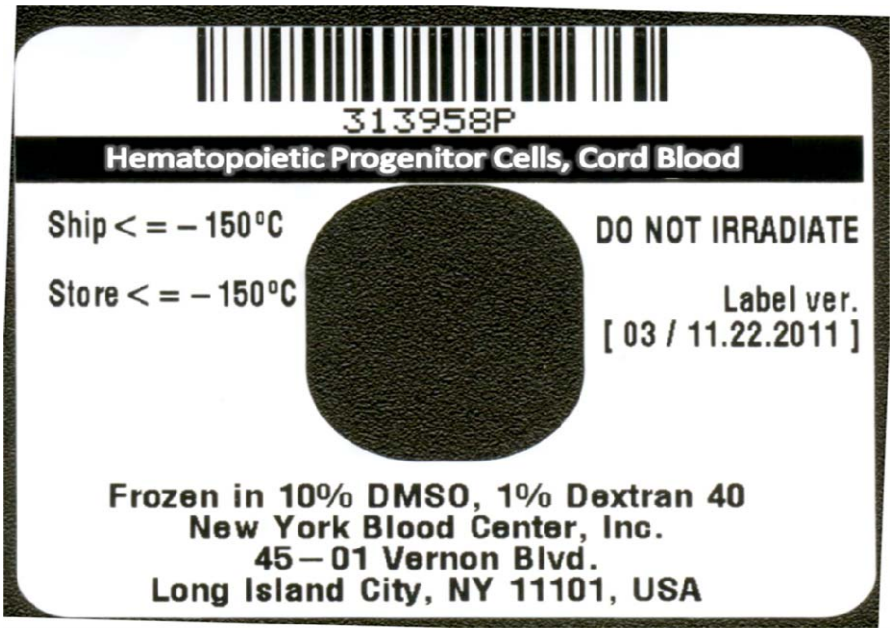
NYBC will affix a label to the cryobag that will not include the product name HEMACORD or the license number, because at the time of freezing it is not known if all the licensure criteria will be met. This label will include a version number in order to comply with FACT standards. The label is designed with a hole in the center for the temperature probes in the BioArchive system which must directly touch the cryobag.

At the time an HPC-C unit is selected from the registry, the unit is retrieved in the BioArchive and segments removed for various product testing. For HPC-C that meet licensure criteria, a new overwrap will be applied to the cryobag. This overwrap will have an affixed container label with the HEMACORD name and license number.

Samples of the labels to be affixed to the cryobag and overwrap are shown in Figure 8.

Package
The package label for Hemacord will be an 8 1/2 x 11" sheet provided as the cover for the other accompanying records. A sample container label is shown in the Figure 9.

FIGURE 3: Example of Labels for Freezing Bag and for Overwrap
Label affixed to cryobag:



Label affixed to overwrap at the timing of shipping a licensed HPC-C:

123456P

Hematopoietic Progenitor Cells, Cord Blood

HEMACORD

Do Not Irradiate

Frozen in 10% DMSO, 1% Dextran 40
Ship: ≤ -150°C
Store: ≤ -150°C

License No .....

New York Blood Center, Inc.
45-01 Vernon Blvd.
Long Island City, NY 11101
USA

FIGURE 4: Package Label

HEMATOPOIETIC PROGENITOR CELLS, CORD BLOOD

HEMACORD

Injectable Suspension

HEMACORD ID: 123456P **NDC 76489-001-01**

RECIPIENT: Last, First **SEARCH ID:** 11111

TNC/kg: 2.3×10^7

HLA match with recipient: one B locus mismatch
(HLA matching is assigned considering low resolution typing for HLA class I A and B loci, and high resolution typing for HLA DRB1 alleles.)

For Intravenous Administration Only

Do Not Irradiate

Rx only

Cryopreservative (concentration): DMSO (10%) / Dextran 40 (1%)

Volume: Approx. 25 mL

Storage: ≤ - 150°C

Expiration Date: 10/11/2020

Warning: This product is made from human cord blood. The risk of transmitting infectious agents is present. Careful donor selection and available laboratory tests do not eliminate the hazard. *(See package insert for Full Prescribing Information on HEMACORD)*

License No. ……

NEW YORK BLOOD CENTER, Inc.
45-01 Vernon Blvd
Long Island City, NY 11101
USA

Reviewer Comment: *The labeling controls in place are acceptable.*

Cord Blood Donor Tracking:

In the delivery room, the mother's identity is confirmed and the container holding the placenta/cord and the collection bag is labeled with the mother's hospital identification label. After collection, if the unit meets the initial qualification criteria, a unique identification number (ID #) is assigned to the unit. The unique identification numbers are in -----(b)(4)------ and pre-printed on colored label sets. The sets also include labels designated specifically (ID# + the suffix "M") for the maternal specimens that are collected for the infectious disease testing. The ID # is both visually and machine readable (bar-coded) and is placed on the collection bag and all the associated collection/Data forms and shipping lists.

In cases of multiple births, the first newborn is labeled by the hospital as twin A and the second one as twin B. Furthermore, for twin deliveries with a single placenta, hospitals will use color or style coded clamps to identify each newborn. If the delivery involves two placentas, each is placed in a separate labeled container in the delivery room prior to transport to the collection area. After collection, each qualified cord unit is assigned a separate ID# (first/lower # is assigned to twin A, next sequential # is assigned to twin B). The collection form contains a section designated for identification of the units in multiple birth settings. One form is completed for each qualified cord unit.

To maintain linkage, the unit ID# is recorded in mother's and infant's hospital records. Mother's identity information is also recorded on the last page of the data form and is maintained at the NCBP database for future reporting of the infectious disease test results. The unique ID# is maintained on all the processing records, associated retained samples, product container labels, test results, registry database and all the unit reports provided to the transplant centers. The unique donor identifiers would allow tracking from donor to recipient and vice versa.

Reviewer comment*: The described tracking method is acceptable.*

CONTAINER CLOSURES AND LEACHABLES

Sponsor has submitted a cross-reference letter from Thermogenesis authorizing the agency to reference the Thermogenesis AXP AutoXpress Platform and the AXP processing kit 510 (k) BK 070006, including the information on supplier of the container/closure, description and identification of construction materials, evidence of integrity testing, biocompatibility/toxicity, and sterilization information to support the BLA Application. Also see DMPQ review.

Collection Bag

Cord blood is collected into a ----(b)(4)---------- collection bag with a non-pyrogenic fluid path, which is 510 (k) cleared by the agency. The bag is manufactured by ----------(b)(4)---------- sterilized by the manufacturer.

Processing Bag Set

The AXP processing bag set is a single-use functionally closed system which is 510 (k) cleared for use in combination with the Auto Xpress Platform. It is supplied by Thermogenesis. The bags are sterilized by --(b)(4)-- performed by the bag manufacturer.

Transfer Bags

A 300 ml or 600 ml Transfer Pack Container with coupler is used to split the fresh cord blood when it exceeds the volume capability of the collection bag. The Transfer Pack is a single bag set, sterile with non-pyrogenic fluid path manufactured by (b)(4). The manufacturer uses –(b)(4)--- to sterilize the packs. The packs are FDA approved for processing and/or storage of blood or blood components

TABLE 8: Containers used in Processing

Product	Vendor	Cat #	Regulatory Status
Collection Bag	-------(b)(4)---------- ----------	----(b)(4)------	510 (k) Cleared
Processing Bag Set	Thermogenesis	----(b)(4)------	510 (k) Cleared
Transfer Bag	----(b)(4)---	----(b)(4)------ ----(b)(4)---	510 (k) Cleared

CONTROL OF ASEPTIC MANIPULATIONS

Control measures which minimize contamination of the HPC-C are contained in SOPs for the various processes. These measures ensure correct identification of the HPC-C and associated samples and prevent collection of cord blood from mothers with high risk for active infections. The various measures are summarized below.

Aseptic Processing Validation (Media Fill)

See DMPQ review for complete review. A summary is documented here.

The aseptic process validation was completed according to protocol NCBP-VAL-10-002P, and the results documented in the validation report NCBP-VAL-10-002R1.

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

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

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

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

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

Collection Facility*:*
Cord blood collection takes place in a dedicated laboratory facility in/or near the Hospital Labor and Delivery area. The laboratories are monitored and access-controlled by NCBP staff.

Collection Procedure*:*

- Mother's medical records are reviewed for high risk CB units exclusion.
- Placentas are cleaned and disinfected before venipuncture, following the procedure used for arm venipuncture during a standard blood donor collection.
- Sterile pyrogen-free disposable blood collection bags are used to collect the cord blood.
- Lot numbers and expiration dates for each collection bag is documented and linked to the HPC-C to allow tracking.
- Dedicated, trained, and properly gowned staff perform the collection using aseptic technique and collecting one unit at a time. Competency for aseptic manipulation for the staff is reviewed annually.

Transport to NYBC (SOPs CB37.0011.1 and CB37.0012.1):
Designated packing and shipping containers follow OSHA standards for shipping human blood. Collected cord blood units are individually enclosed in biohazard bags and wrapped with absorbent pads. They are shipped at room temperature with continuous monitoring of temperature. Completed data forms (donor screening questionaire) and maternal blood specimens are sent with the same shipment within separate, protected containers.

Receiving at NYBC (SOP CB38.0001.1):
Collection bags are inspected for integrity before used.

Processing:
The overall process takes place in distinct unit operations (processing, cryopreservation and freezing) performed in physically segregated, controlled and monitored environments.

The AutoXpress bag set is the ----------(b)(4)---------- . The bag set is disposable and for single-use, with a sterile, non-pyrogenic fluid path. The sets are sterilized by the Manufacturer by ----(b)(4)---------- sterile connecting device is used to connect the tubing of the kit.

DMSO cryoprotectant, the only reagent added to the processed HPC-C, is added via an integral 0.2 micron filter under a Biosafety cabinet. It comes in single-use sterile (b)(4) vials. The vials are ---(b)(4)---- until inspected, tested and released to a different ---(b)(4)---- after tagging as "release for use". The lot number, expiration dates, and name of manufacturer are recorded for each HPC-C. In-process samples are collected by ----------(b)(4)----------.

Non-conforming HPC-Cs are removed from inventory after review.

Storage and retrieval of HPC-C from liquid nitrogen freezer is recorded automatically in the BioArchive computer (includes time retrieved and returned).

Specific operational limits for processing times are defined; e.g. cord blood processing is completed within ---(b)(4)-- of collection, and freezing is completed within -(b)(4)- after adding cryoprotectant.

Containment between rooms is achieved by airlock, and pressure differences; airflow is away from area requiring greatest level of segregation. Pass-through windows are used to transfer product and samples. The liquid levels of the liquid nitrogen freezers, oxygen levels in the air, as well as the temperature and humidity of the manufacturing areas are continuously monitored by an automatic alarm system ----------(b)(4)---------- (SOP CB00.0006.1). Equipment used in manufacturing is routinely inspected and calibrated.

Personnel:
Only personnel with proper training in aseptic processing perform the steps in aseptic manufacturing process. The Technologists are regularly evaluated for adherence to aseptic processing procedures.

ENVIRONMENTAL ASSESSMENT
The applicant claims categorical exclusion from environmental assessment based on 21 CFR 25.31(c).

COMPUTER SYSTEM

Note: The computer system and interfaces were reviewed by DMPQ.

The NCBP Application Enterprise System (NAES) integrates and coordinates NCBP's business processes. The NAES core is a centralized data repository (Oracle Database Management System) which stores information from and supplies to the application components. It has a multi-tier architecture, application logic partitioned among various servers and components based on Microsoft and Oracle environment and infrastructure. The NAES also manages various aspects of operations including:

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

All the major steps of processing as well as all test results, searched for matched HPC-Cs and patient information, are recorded in the company's Oracle database. The computer system includes back-up and disaster recovery servers that can restore all information entered and saved, in the event that data becomes unavailable from the primary server. The backup is updated concurrently and automatically (mirrored) with the primary database, while the disaster recovery server, resident extramurally, is updated -(b)(4)-. The systems are redundant and are tested at regular intervals.

ACCESS TO NCBP HPC-C INVENTORY

Transplant centers or registries can make a search request for a HPC-C through NCBP's WebSearch application, or through a 'Single Point Access' of the National Cord Blood Inventory (NCBI), or directly by fax to NCBP.

NCBP WebSearch Application:

The WebSearch is an online transactional search tool for HPC-Cs. It allows access to transplant centers and registries to perform real-time searches of the NCBP inventory, view HPC-C information, enter specimen request, arrange shipments and communicate with NCBP through an internal communication system. The requests that are processed include:

1. Receiving and responding to email alerts from transplant centers regarding all patient transactions
2. Receiving and processing HPC-C HLA typing confirmatory requests.
3. Monitoring DNA specimens request from the HPC-C and/or mother; this includes HPC-C DNA request for HLA typing and record keeping of HLA typing results and all samples shipped.
4. Monitoring additional testing and eligibility determination requests.
5. Processing shipment requests.

The WebSearch application is accessed by logging into the following website: https://nybc.placentalblood.org/NYBCLogin.aspx

Users, including NCBP staff login to the site via a USER ID and 'password'. The HLA type of patients registered in WebSearch is used to search for a matched HPC-C, and when a match is found, its NCBP or NMDP identification number is used to review its information. Notifications to requests are communicated via email in WebSearch. These notifications include requests to register a new patient, to reserve a HPC-C, to request a confirmatory HLA typing, and/or to arrange shipment. Additional testing or samples (maternal of cord blood) may also be requested by the transplant center or registry.

Donor eligibility (DE) is made before HPC-Cs are released into the Search Inventory. The Medical Director or Director of Donor Services reviews and makes DE determination; eligibility results are available overnight. A notification for shipment request is made by email to NCBP and arrangements are made to ship the unit.

Reviewer Comment*: The computer system was reviewed by DMPQ during inspection. It was discovered at the time that DE determination was being made after a HPC-C is entered into search inventory. NCBP was cited on the 483 for this practice. Issue has been addressed in the response to the 483 citation, and DE is now made prior to release of HPC-C into search inventory. Sponsor is aware that ineligible units will not be licensed; they may be used under urgent medical need under IND.*

Single Point Access of the National Cord Blood Inventory (NCBI)

The SOP CB41.003.1 addresses how NCBP communicates with the US registry, National Marrow Donor Program (NMDP)'s CordLink application to exchange HPC-C information and process search requests from NMDP; CordLink is the web access to the NMDP inventory.

NCBP personnel who are authorized to use CordLink access the application ----------(b)(4)----------. Sponsor reports that CordLink can be accessed at:

----------(b)(4)----------
Reviewer Comment*: website cannot be found/accessed.*

Note: During inspection, Sponsor explained that the website is accessed by authorized personnel only.

When NMDP registry requests for a confirmatory typing on a HPC-C via email, NCBP coordinator verifies the availability and the NCBI status of the HPC-C in the Oracle computer. If the unit is available, a confirmatory typing is requested.

To hold /reserve a unit, NMDP/Transplant Center notifies NCBP via email to request the hold. The unit may then be ordered after the hold and processed for shipment. Three forms (Product Insert Packet) are generated to accompany the shipment.