MEMORANDUM

BLA 125391
CMC Review of Original Submission
HPC, Cord Blood

ClinImmune Labs, University of Colorado Cord Blood Bank

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

Reviewed by:	Signature
Yong Fan, MD Review Committee Chairperson	
Lilia Bi, Ph.D.	
Fatima Abbasi, MS	
Joydeep Ghosh, Ph.D.	
Safa Karandish	
Concurred by:	
Keith Wonnacott, Ph.D. **Branch Chief**	
Kimberly Benton, Ph.D. **Deputy Division Director**	
Raj Puri, M.D., Ph.D. **Division Director**	

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EXECUTIVE SUMMARY

Recommendation:

We recommend that BLA 125391 be approved. The approval should be granted only for the HPC, Cord Blood lots that will be manufactured after the approval date.

The applicant initially requested licensure of HPC, Cord Blood lots in inventory since July 20, 2005, using both ----------(b)(4)---------- methods to partially reduce the red blood cells (RBCs) and plasma. After review of the application and inspection, the review team has determined that the existing inventory does not meet licensure requirements because the applicant did not demonstrate CGMP compliance until the date of approval
The applicant also submitted a major amendment during the last three months of the review therefore the action date was extended from March 2 to June 2, 2012.

Product Overview

HPC, Cord Blood manufactured by ClinImmune Labs, University of Colorado Cord Blood Bank (UCCBB) are minimally manipulated human cord blood cells. The applicant uses the ----------(b)(4)------ to reduce the plasma volume and the RBCs for most of the cord blood units (CBUs) collected. ----------(b)(4)----------. The final product volume range is between 30 to 124 mL and depends on the processing method used and the volume collected. HPC, Cord Blood is cryopreserved in 10% DMSO containing 1% Dextran 40 using the ---(b)(4)--- freezer and stored in either the vapor or liquid phase of the liquid nitrogen freezer after purity, identity, sterility and potency tests.

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

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

The applicant will include thawing instructions with the shipments and the thawing method has been validated.

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

Review Findings

The review team identified multiple deficiencies during review and inspection. All deficiencies were communicated to the applicant through letters, teleconferences and during inspection. Examples of major deficiencies include inappropriate donor eligibility determination procedure, deficient quality system and batch records, insufficient processing and assay validations and insufficient processing controls. The applicant corrected all deficiencies and amended the application to the satisfaction of the review team. Based on the review of the information submitted in the original submission and 8 amendments, the review team has determined that the HPC, Cord Blood manufactured by the applicant now meets all the CGMP requirements and recommendations of the cord blood licensure guidance; therefore, the review team recommends approval of this BLA.

GENERAL INFORMATION

The applicant, ClinImmune Labs, is an affiliate of the University of Colorado School of Medicine and is comprised of the Histocompatibility Laboratory, the UCCBB, and the Stem Cell Laboratory.

The main facility is where the CBUs are received, processed, cryopreserved, and stored in quarantine. The quality tests are performed at UCCBB, Stem Cell Lab, and other contract facilities as listed under testing facilities below and in testing section. The applicant is American Association of Blood Banks (AABB) accredited and the Stem Cell Lab is College of American Pathologist (CAP) and Foundation for the Accreditation of Cellular Therapy (FACT) accredited. HLA lab is American Society for Histocompatibility and Immunogenetics (ASHI) accredited. The main facility is located at:

12635 E. Mountview Blvd, Suite 300 and 360
Aurora CO 80045
303-724-1306
FEI# 3000719046

The permanent storage facility is located at:

1999 North Fitzsimmons Parkway, Suite 160
Aurora, CO 80045
303-724-1306
FEI# 3009078636

Table 1: List of Testing Laboratories

Lab name and location	Tests performed	Certificates/Accredits
ClinImmune Lab, Hematology Laboratory, Room # 305	Total nucleated cells count	CLIA, FACT
	---(b)(4)--- viability	
	----------(b)(4)---------	
ClinImmune Lab, Histocompatibility Laboratory, Room # 302	HLA typing	CLIA, ASHI, CAP
Colorado Department of Health (DOH)	Hemoglobinopathy test	CAP and CLIA
University of Colorado Hospital Clinical Blood Bank	ABO Rh blood type	AABB and CAP
----------(b)(4)----------	Infectious disease testing	CLIA, AABB, CAP
University of Colorado Hospital Clinical Microbiology Laboratory	Sterility testing	CLIA, CAP

Intended Use:

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

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

BACKGROUND/HISTORY

ClinImmune Labs, UCCBB is the manufacturer of HPC, Cord Blood under this license application.

The applicant has 14 years history of cord blood banking prior to the submission of this BLA. Prior to the use of the ------(b)(4)------ processing method on January 30, 2007, there were (b)(4) HPC, Cord Blood ---(b)(4)--- processed and banked. The applicant is seeking licensure of the HPC, Cord Blood units that are manufactured using both ---------(b)(4)--------- methods. Inventory that does not

meet licensure requirements will be distributed under IND (b)(4) which is sponsored by the National Marrow Donor Program (NMDP).

FACILITY DESCRIPTION AND FLOOR DIAGRAMS

The main facility consists of class -(b)(4)- clean rooms equipped with class (b)(4) Biological Safety Cabinets. The main facility is where all the CBUs are accessioned, processed, cryopreserved, and quarantined after collection. Collected CBUs are received and accessioned in room (b)(4). The accompanying documents including preliminary donor screening and donor information are also reviewed by the bank staff here. The CBUs then are transferred into room (b)(4) for volume determination before processing in room -(b)(4)--. The pre and post processing samples are tested in room (b)(4) for TNC and ---(b)(4)--- viability. The processed HPC, Cord Blood lots are cryopreserved in room (b)(4) using the -----(b)(4)----- freezer and quarantined in liquid nitrogen freezer located in room (b)(4). The HPC, Cord Blood lots are transferred to the permanent storage facility when all release criteria are met after the completion of release tests and batch records review.

The permanent storage facility is approximately 2 miles away from the main processing facility. Facility access is only permitted with controlled security card readers. ----------(b)(4)----------.

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

HPC, Cord Blood DESCRIPTION

HPC, Cord Blood manufactured by the ClinImmune Labs, University of Colorado Cord Blood Bank (UCCBB) is a minimally manipulated allogeneic cord blood hematopoietic progenitor cell therapy product.

The applicant has contracts with hospitals in Colorado and Arizona for collection of cord blood. ClinImmune also uses a statewide, non-fixed site collection program.

Cord blood collection is performed in-utero before the delivery of the placenta in the hospital's labor and delivery area. After collection, the bag is transported at controlled room temperature ((b)(4)) to the bank for processing and cryopreservation.

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

The processed HPC, Cord Blood is cryopreserved in 10% DMSO containing 1% Dextran 40 using a ----(b)(4)---- freezer, and stored in quarantine in (b)(4) freezer (vapor phase). The final

products are transferred to the permanent storage facility and stored at ≤-150°C after all release criteria are met. After transfer to permanent storage, HPC, Cord Blood is listed in a searchable database so that the transplant centers and transplant registries can match the HPC, Cord Blood with patients who need transplants.

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

Proprietary Name: The applicant did not request a proprietary name

Non-proprietary Name: HPC, Cord Blood

Active Ingredient:
CORD BLOOD HEMATOPOIETIC PROGENITOR CELLS
UNII Code: 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 #: The applicant requested an NDC code exemption because the applicant uses the ISBT 128

The ISBT 128 facility code: W3213
The ISBT 128 product code: S1393

CONTAMINATION PRECAUTIONS

(Please also see CGMP review by division of Manufacture and Product Quality)

In-process controls

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

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Reviewer's Comment:

Although the applicant claimed the above measures were sufficient to prevent contamination, the review team identified deficiencies related to validations and cGMP compliance during review and inspection. The applicant corrected the deficiencies and the corrections are acceptable to the review team.

QUALITY PROGRAM

(Please also see CGMP review by division of Manufacture and Product Quality)

The applicant provided a Quality Management (QM) Plan Overview SOP. The QM team includes managers, directors, and physicians and meets (b)(4) to discuss deviations, validation, audits, contracts, proficiency testing, and process improvement.

Reviewer Comment:
This QM team concept was designed to meet AABB and FACT standards, and did not initially meet the cGMP requirement described in 21 CFR 211.22. Specifically, the quality program was not independent and the final CBU release for transplantation was approved by medical director, bank director and laboratory director. The cGMP regulation requires an independent Quality unit to objectively approve or reject products. This was a 483 citation item and the applicant has corrected this deficiency. These deficiencies were resolved through amendments to the BLA and the quality unit is now independent and has appropriately defined responsibility and authority.

DONOR ELIGIBILITY DETERMINATION

Donor eligibility procedures include screening and testing of the cord blood donors for risks of communicable diseases or disease agents. Birth mothers go through an initial qualification process prior to the collection of the cord blood unit. The following are the initial exclusion criteria:

- Multiple births
- Less than 35 weeks gestation
- Surrogate birth mothers

In-utero cord blood collections are performed at five (5) fixed collection sites and also at non-fixed (statewide program) collection sites. The process for the initial qualification and screening of the birth mother at the fixed and non-fixed collection sites are summarized in the Donor Screening section below.

Donor Screening

The donor screening process includes the review of the birth mother's and baby's medical records, including physical examination records, and the maternal risk questionnaire to identify risks for relevant communicable disease agents or diseases. Any risk factor identified during the

review of the donor questionnaires and the relevant medical records may disqualify the birth mother from donation of the cord blood unit.

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

   The applicant has established agreements with the collection hospitals. ClinImmune's trained staff is responsible for obtaining consent from the birth mother and performing the initial donor risk assessment. Birth mothers who have passed the initial risk assessment must complete the Family Medical and Maternal Risk Questionnaires. The applicant utilizes the standard NMDP donor questionnaires. The donor consent, completed questionnaires, and a copy of the medical and physical examination records for both the birth mother and the baby are sent to ClinImmune for review and completion of the final donor eligibility determination.

2. Birth mother pre-qualification and donor screening at non-fixed collection sites

   Preliminary donor information and health assessment are obtained over the phone. If the birth mother meets the initial acceptability criteria, a Doctor/Midwife Cord Blood Collection Agreement is emailed to the birth mother to present to her physician. The agreement includes instructions for collection (including a link to the training website). Physician must sign the form and agree to provide the medical and physical examination records (birth mother and baby) to ClinImmune. After the signed agreement is received by ClinImmune, a packet containing the consent form and the family medical and maternal risk questionnaires are mailed to the mother. After receipt of the completed forms, a trained ClinImmune staff contacts the mother to review the questionnaires. If the birth mother meets the acceptance criteria, collection supplies, physician instructions for collection of cord blood and maternal blood specimens, labels and other associated forms are sent to the mother. At the time of delivery, a health update status form is completed by the birth mother to document any changes to the maternal risk questionnaire and health status. After completion of the cord blood collection, the completed forms, a copy of the medical records and the maternal blood specimens are shipped to ClinImmune along with the collected unit. If a copy of the medical records is not shipped with the collected unit, ClinImmune requests the records directly from the hospital.

   Donors are screened for the following risk factors:

   HIV 1/2, HTLV I/II, HBV, HCV, syphilis, WNV, sepsis, vaccinia, TSE (CJD/vCJD), xenotransplantation

   Additionally, donors are screened for --(b)(4)--, -(b)(4)-, and ---(b)(4)---, which are not currently required by the FDA.

   Reviewer Comment:
   Donor screening is performed in accordance with the donor eligibility (DE) regulations and the recommendations in the DE guidance (August 2007).

Donor Testing

1. Testing Lab:
   All donor infectious disease tests are performed at ----------(b)(4)----------.

2. Testing lab qualification:
   The contract testing laboratory is registered with the FDA, is CLIA certified (certification # provided) and accredited by AABB.

   ClinImmune reviews the documentation of competency, proficiency, quality program, and the accreditation of the contract laboratory.

   The applicant has submitted examples of the infectious disease test system's Installation, Operation, and Performance Qualification reports as well as a summary of the proficiency tests performed in 2010 and 2011 by the testing laboratory. The summary indicates that the results of all the proficiency tests were acceptable.

3. Test samples:
   Maternal blood specimens for donor testing are obtained on the day of or within 7 days of the infant's birth. The blood collection tubes are labeled with a unique identification number including a barcode (refer to the Cord Blood Donor Tracking for additional information). Maternal blood specimens are sent to the cord blood bank along with the collected cord blood unit and are maintained at temperature between 15-25^{o}C during transit. ClinImmune tracks receipt and shipment of the maternal blood specimens to the testing laboratory.

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

Table 2: Donor Infectious Disease Tests

Test	Test kit Manufacturer	Test	Test kit Manufacturer
(b)(4)-HB-	---------(b)(4)----------	(b)(4) HIV/HCV/HBV	---(b)(4)---
HB(b)(4)	---------(b)(4)----------	Treponema pallidum	---(b)(4)---
(b)(4)HCV	---------(b)(4)----------	(b)(4)CMV	---(b)(4)---
(b)(4) HIV 1 and 2	---------(b)(4)----------	(b)(4) WNV	---(b)(4)---
(b)(4) HTLV I and II	---(b)(4)---	----(b)(4)----	---------- ----(b)(4)----------

Reviewer Comments:
The applicant discards HPC, Cord Blood lots that are collected from birth mothers who test positive for any of the above tests except for CMV. CMV results are reported to the transplant center but the results are not factored into the donor eligibility determination.

The applicant also discards HPC, Cord Blood lots that are collected from birth mothers who have been ----------(b)(4)----------.

Licensure is being recommended for the HPC, Cord Blood lots that are manufactured after the BLA approval. Therefore, all the HPC, Cord Bloods in the existing inventory will be released under an IND. The donor testing performed for units that were manufactured prior to the approval of the BLA is not included in this review.

Final Donor Eligibility Determination

The applicant's process for determining donor eligibility includes 3 stages. At any stage, a decision can be made to exclude a donor and discard the unit. Units are maintained in quarantine until the final donor eligibility determination has been made by the Medical Director.

The following are the 3 stages of donor eligibility:

- Preliminary review of maternal donor history, consents and physical examination
- Review of donor information at receipt at the processing facility to assure identity and acceptability
- Final review of all the screening and testing results and sign-off by medical director

Donors are deemed to be eligible if the donor screening does not identify any risk factor for communicable diseases agents or diseases; and all the infectious disease test results are negative or non-reactive (except for CMV). Only units collected from eligible donors are qualified for licensure. The summary of records (Form E5.103.14), that accompanies the HPC, Cord Blood at the time of distribution, includes the listing and interpretation of all the infectious disease tests.

Note: *After the BLA approval, the applicant will only bank units that are collected from eligible donors.*

For cord blood units collected after May 25, 2005 but prior to the BLA approval, donors are deemed to be ineligible if the donor screening identifies a risk factor for communicable disease agents or diseases. Cord blood units collected from donors for whom donor eligibility has not been completed (e.g. incomplete maternal risk questionnaire, testing not performed using FDA-licensed, approved or cleared tests) or from ineligible donors are used under an IND if there is a documented urgent medical need.

The final donor eligibility status is entered into the Cord Blood Bank Manager (CBBM) database for final review and sign-off by the Medical Director.

Reviewer Comment:
The procedure for the final donor eligibility determination is in accordance with the donor eligibility guidance (August 2007), and is acceptable.

CORD BLOOD COLLECTION

The applicant currently collects CBUs from five (5) fixed collection sites located in Colorado and Arizona (listed below) and also at non-fixed collection sites (statewide program within the state of Colorado) using in-utero collection procedure (prior to the delivery of the placenta).

Collection Sites

(1) Exempla St. Joseph's Hospital
1835 Franklyn St.
Denver, CO 80218-1126
970-495-8710

(2) Denver Health Medical Center Hospital
1777 Bannock St.
Denver, CO 80204
303-837-7270

(3) Maricopa Medical Center
2601 E. Roosevelt St.
Phoenix, AZ 85008
303-602-9715

(4) St. Joseph's Hospital and Medical Center
350 West Thomas Rd.
Phoenix, AZ 85013
602-406-3000

(5) Phoenix Baptist Hospital
2000 W. Bethany Home Rd.
Phoenix, AZ 85015
602-249-0212

Collection Procedure

1. **Preparation of collection kits and documents**
   ClinImmune's staff prepare the collection kits, which include the collection bag and sample tubes for testing etc., generate labels and appropriate documentations (forms), and send them to all five fixed collection sites.

   For non-fixed sites, ClinImmune screens potential donors on the phone and sends the collection kits and forms to potentially eligible donors. The donors must have collectors that sign and return collection agreements and training confirmation to ClinImmune. Donors bring the collection kits and forms to the JCAHO accredited hospitals during delivery.

2. **Collection site qualification**
   The collection facility will have sufficient space and personnel for appropriate preparation and storage of collection supplies and equipment. A separate area will be designated for temporary storage of the product after collection and before transport. The collection site medical director is designated to provide donor review of adverse reactions reports.

3. **Collection reagents and supplies (see Table 3 below)**
   All reagents and supplies are labeled as "quarantined, received" and stored separately before being qualified for use. All reagents undergo lot-to-lot and shipment-to-shipment testing (the new lot is compared with the one that is currently in use). If the item is qualified based on the Certificate of Analysis and expiration date, and meets acceptance criteria, the quarantine sticker is removed and replaced with a sticker containing the following: item name, lot number, expiration date, storage temperature, release date, open date, and staff initial. For non-critical supplies that do not contact the cord blood and for which the vendor does not provide an expiration date, the sponsor assigns an expiration date.

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

Table 3: Cord Blood Collection Reagents and Supplies

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

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

4. Collection staff training

All employees are initially trained to perform all collection steps and competency is assessed annually. The applicant monitors volume and sterility and retrains collection staff when necessary (when more contaminated units or more units with lower volumes occur).

For the non-fixed sites, ClinImmune provides training materials including collection, consenting, and donor screening/testing SOPs and a video to visually demonstrate the collection procedure. The collectors must sign a document that is provided by ClinImmune to confirm that they have been trained to perform the collection.

5. Consenting and preliminary donor screening

Please see donor eligibility determination review section

6. Cord blood collection

All collections are performed prior to the delivery of the placenta (in-utero) regardless of vaginal delivery or c-section. The collection staff check the donor ID by matching the paper work with the arm band, disinfect the umbilical cord using ---(b)(4)---, insert the needle and drain the cord blood into the collection bag.

CBUs are collected from mothers who are at least 16 years old, 35 weeks gestation, and singleton birth. The birth mothers are contacted to follow-up with baby's health status 6 months post donation. The collection staff also collect and label maternal samples for infectious disease testing during cord blood collection.

The collected CBUs are shipped to ClinImmune for processing. The storage, shipping condition, and acceptance criteria for processing are the same for the CBUs that are collected from both the fixed sites and non-fixed sites.

7. Labeling, storage and transportation

The applicant uses a bar coding system for labels. All labels are generated by the applicant's staff and shipped to the collection sites along with the assembled collection kits including the relevant documentations. The collection staff fill the labels with the collection date and time, collection facility, cord blood volume, anticoagulant volume, and expiration date and time (48 hours post collection). The collection staff also place a biohazard warning label (product may transmit infectious agents).

The applicant uses ISBT128 label for cord blood banking.

The collected cord blood and test tubes are stored at the collection facility and shipped back to the applicant in validated shipping containers at (b)(4) for further processing. All CBUs that meet acceptance criteria are processed with (b)(4) of collection and subsequently cryopreserved.

Reviewer Comments:
In general, the non-fixed site collections are not as efficient as those performed at fixed sites because of the low frequency. However, the applicant has banking criteria and the CBUs that do not meet the banking criteria will be discarded.

Based on the above assessment, the reviewer concludes that the collection procedures for both fixed and non-fixed collection sites are acceptable.

Collection Procedure Validation

The validations submitted initially were not acceptable because they were not really validations, but rather retrospective data analyses. The applicant performed a new collection validation as requested by the review team during the review and this validation report was submitted with Amendment 3.

1. **Validation plan:**
   ----------(b)(4)----------

2. **Validation outcome:**
   All evaluated parameters met the predefined criteria (see Table 4 below)

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

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

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

Reviewer Comment:
The CBUs that were used for this validation were collected from the fixed collections sites only. However, the procedures including donor consenting, screening, and the collection are the same. The non-fixed sites are also accredited by JCAHO and the collectors are trained. In addition, the applicant has banking criteria to disqualify the units that do not meet licensure requirements. Therefore, the reviewer determines that this is a successful validation.

Collection Shipping Container Validation

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

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

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Validation results:
----------(b)(4)----------
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----------(b)(4)----------
----------.

Reviewer comment:

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

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The validation data, the temperature monitoring and acceptance criteria that are in place are acceptable.

CORD BLOOD PROCESSING

Overview

The applicant currently uses two processing methods, ----------(b)(4)---------- methods. ----------(b)(4)----------. Both methods are designed to reduce the RBCs and plasma volume by ----------(b)(4)----------. The plasma volume reduction is achieved by ----------(b)(4)----------.

Most of the CBUs are processed using the ----------(b)(4)----------.

Reagents and Supplies

Table 5. Processing Reagents and Supplies

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

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

Reviewer Comment:
----------*(b)(4)*----------.

In-Process Testing (Banking Criteria)

The applicant performs in-processing testing to determine whether or not a CBU is suitable for banking. The table below (Table 6) shows the testing performed and acceptance criteria for banking.

Table 6. In-process Testing

Parameters	Sample	Test method	Acceptance criteria	Comment
(b)(4)	-------(b)(4)--	----------(b)(4)----------	(b)(4)	
TNC	Post processing	----------(b)(4)----------	$0.5x10^9$	
Viability	Post processing	-----(b)(4)-----	(b)(4)	
CD34+ count	Post processing	-----(b)(4)-----	$>1.25x10^6$	
Sterility	Post-processing	(b)(4)	Negative	
DE	Screen & test	Vary	Eligible	
Hemaglobin	Baby blood	------------(b)(4)----------	No homozygous abnormality	
Processing time			(b)(4) from collection	(b)(4) from collection to freezing
(b)(4)	------(b)(4)--------	------------(b)(4)----------	(b)(4)	

Reviewer Comments:
The applicant stated in the original submission that "CBUs that do not meet the criteria above will be reviewed by a lab medical director or lab director and can be considered for permanent storage if validated". However, the applicant did not explain the rationale of banking the CBUs that do not meet the release criteria or the circumstances of releasing these CBUs to transplant centers.
This issue was conveyed in FDA day 74 letter and the applicant clarified that the "non-conforming units" will be banked and released under the NMDP IND (IND(b)(4)) only.

HPC, Cord Blood Processing:

1. **---(b)(4)--- method processing using ---(b)(4)---**
   ----------(b)(4)----------
   ----

4 pages redacted (b)(4)

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

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

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

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---***(b)(4)***----------
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---***(b)(4)***----------
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The data support that the ------(b)(4)------ methods reliably produce HPC, Cord Blood products that will meet release criteria.

CRYOPRESERVATION AND STORAGE

The --(b)(4)-- is mixed with cryoprotectant consisting of 10% DMSO and 1% Dextran 40, and transferred to a cryopreservation container. The applicant uses ----------(b)(4)---------- are FDA 510(k) cleared medical devices. ----------(b)(4)----------. The final product is cryopreserved using the ----------(b)(4)---------- freezer ((b)(4)).

Cryopreservation Procedure:

Freezing program (----------(b)(4)----------)

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

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----------(b)(4)----------.
Cryopreserved HPC, Cord Blood is placed in an overwrap and a metal canister that protects the bag after cryopreservation. The product is temporarily stored in quarantine in a vapor phase of a liquid nitrogen freezer until records reviews are completed and bankable/searchable determinations are made. The product is then transferred using a monitored dry shipper to the liquid nitrogen storage freezer at a separate location for permanent storage in either liquid or

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Reviewer Assessment:
This validation is adequate.

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Reviewer Assessment:
This validation is acceptable.

FINAL LOT RELEASE TESTING

Listed below in Table 10 is a summary of the lot release tests that are performed on each HPC, Cord Blood lot, the acceptance criteria, and test methods used. Infectious disease testing is performed on a maternal blood sample, hemoglobin analysis and ABO/Rh typing are done using pre-processing cord blood samples, and the rest of the testing is done on post-processing HPC, Cord Blood samples.

Table 10: Lot Release Acceptance Criteria for HPC, Cord Blood

Product Characteristics	Testing/ inspecting	Criterion	Test Method
Safety	Infectious disease- 21 CFR1271.45-90	All tests negative except for CMV results which are recorded. *Performed on maternal blood sample within 7 days of birth [21 CFR 1271.80 (a)(b)].*	Performed by --------- (b)(4)-------- using FDA licensed or approved test kits
	Sterility- Bacterial/fungal cultures	No Growth	Performed by University of Colorado Hospital using the -----(b)(4)----- system
	Hemoglobin	No homozygous hemoglobinopathy	Performed by Colorado Department of Health using FDA cleared test kit.
Integrity	Container, closures, seals	Intact	Visual cord blood bag inspection
Purity and Potency	Total nucleated cells (TNC)	$>5.0 \times 10^8$	Performed by University of Colorado Hospital using the ---(b)(4)--- system
	Viability of TNC	(b)(4)	Performed by the applicant using ---------- (b)(4)----------
	Viable $CD34^+$ cell count	$\geq 1.25 \times 10^6$	Performed by University of Colorado Hospital using ------(b)(4)-------
	----------(b)(4)----------	(b)(4)	----------(b)(4)----------
Identity	HLA typing	Recipient and Donor match level reported	Class I A &B, Class II DRB1Testing performed by ClinImmune Histocompatibility testing laboratory from cord blood sample and a detached segment.
	ABO and Rh	Recipient and Donor match level reported	Performed by University of Colorado Hospital using FDA cleared test kits

Safety Testing

Donor Infectious Disease Testing

(Please see Donor Eligibility section)

Hemoglobin Testing For Homozygous Hemoglobinopathy

1. Screening test

Description:
The blood sample from the baby is tested for hemoglobinopathy. The applicant has set up an agreement with the Colorado Department of Health (DOH) to obtain the testing results on the baby's blood collected in the (b)(4) test tubes at day 3 and confirmed at 4 weeks after birth. The maternal donor agrees to release this information to ClinImmune during the consent process at donation. This consent includes documentation of a state ID number and baby's date of birth. Individual report requests are faxed to DOH and report results are received at the ClinImmune Labs within 3-4 days. The baby's blood is tested from two separate sample draws and both results must be negative for homozygous abnormal hemoglobinopathy to meet banking requirement of the CBU. The Colorado Department of Health submitted their CLIA certification, standard operating procedure, proficiency testing program and staff competency.

DOH stated that the initial validation records are no longer available**.** CMS-CLIA has not requested this test to be revalidated. However, following documents and information were provided:

Test kit:
The -------(b)(4)---------- Kit used to run this assay is 510(k) cleared by CDRH under ---(b)(4)---.

SOP summary:
----------(b)(4)----------

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

QA:
Information of quality assurance policy at Laboratory Services Division of DOH was provided.

2. Confirmation test:

Description:
All abnormal results received at ClinImmune Labs are confirmed by the University of Colorado Hospital Clinical Chemistry Lab (UHCC) on baby's blood samples from the second collection at 4 weeks after birth. The test is performed using ----------(b)(4)---------- Kit. The test SOP is provided. So far all the confirmation test results done at UHCC are consistent with the screening test results done at DOH.

Reviewer Assessment:
Hemoglobin test is done with baby's blood sample at day 3 and confirmed at 4 weeks after birth. The test is performed by using a 510(k) cleared kit with defined testing SOP and proper controls. The test is acceptable.

Sterility Testing

The applicant of BLA 125391 has proposed to use ----------(b)(4)---------- with ----------(b)(4)---------- media for testing the sterility of their processed cord blood final product (HPC, Cord Blood). The test sample for the HPC, Cord Blood sterility assay is --------(b)(4)------ and the proposed incubation time and temperature are ---------(b)(4)---------- respectively.

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

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

Reviewer Comments:
The detection mechanism for the -------(b)(4)------ is significantly different from the compendial methods described under the 21 CFR § 610.12 and the USP <71>. Therefore, under the regulations described under 21 CFR § 610.9(c) the applicant would be expected to demonstrate equivalency of the ------(b)(4)------ to the compendial methods. However, OCTGT's current

policy is that for HPC, Cord Blood products, performance of parallel testing with CFR 610.12 (or USP <71>) as part of the method validation will not be required.

Note:

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Sterility Assay Protocol for Lot Release

The proposed test method and release specifications using ----------(b)(4)---------- to determine the sterility of the HPC, Cord Blood final product is acceptable for this BLA.

Identity Testing

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

HLA Typing

Description:
The HLA Typing is performed at ClinImmune Labs, Histocompatibility laboratory which is CLIA certified, and ASHI and CAP accredited.

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- All goals were met.

Reviewer Assessment:
The verification of HLA test is acceptable.

ABO Blood Group and Rh Typing

Description:

The University of Colorado Hospital Clinical Blood Banking (Transfusion Services) facility performs two ABO/Rh typings on each of the HPC, Cord Blood products. One sample is collected at receipt for processing and a second sample is collected prior to the addition of -(b)(4)-.

Test Verification
Title:
UH Clinical Laboratory-Transfusion Services ABO/Rh Testing of HPC products

Purpose:
To verify that the Clinical Laboratory-Transfusion Services ABO/Rh Testing of HPC products is consistently accurate to ensure a safe product at infusion

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

Conclusion:
Goals were met.

Reviewer Assessment:
The ABO/Rh typing is acceptable.

Potency Testing

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

Total Nucleated Cell (TNC) Counts:

Description:
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Reviewer Assessment:
The TNC validation has not been done as per ICH Q2R1 guidelines and the validation acceptance criteria seem wide. However based on the provided test results, the assay has been shown to be suitable for the intended use.

Nucleated Cell Viability Assay (---(b)(4)---)

Description:

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Reviewer Assessment:

- *The revised frozen-thawed cell dilution procedure and ---(b)(4)---- viability test SOP are adequate.*
- Based on the test results provided in the -----(b)(4)----- viability validation, the test is suitable for the intended use

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

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

Reviewer Assessment:
The (b)(4) assay is highly variable and difficult to standardize. The (b)(4) assay and release criteria are not specified in the FDA cord blood licensure guidance. Most of the banks use "-(b)(4)-" as acceptance criteria for validation and release. The validation data showed ----------(b)(4)--------- therefore, the reviewer concluded that this validation is acceptable.

CD34+ ---(b)(4)--- cell enumeration and viability

Rationale for CD34+ ---(b)(4)--- Cell Enumeration and Viability as part of potency
The CD34+ cell population in cord blood includes hematopoietic progenitor cells. The absolute CD34 count in the product to be cryopreserved is a measure of potential potency. The post-thaw CD34+ cell count of the HPC, Cord Blood product correlates with the speed and probability of post-transplant engraftment. Determination of viable post thaw CD34 positive cells is based on TNC --------(b)(4)---------- and therefore is part of the potency test for HPC, Cord Blood.

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Expected Results
----------(b)(4)----------
---------- The minimum acceptable viable CD34+ cell content of an HPC, Cord Blood product is $\geq 1.25x10^6$.

Description of Protocol

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

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

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

Reviewer Comment:
The applicant has adequately demonstrated the accuracy, precision, linearity, and limits of detection for the ----(b)(4)------ assay of their HPC, Cord Blood product as part of the potency lot release criteria.
Training and Competency: Three operators were trained ----------(b)(4)----------.

Overall Reviewer Assessment for --------(b)(4)----------
The applicant has adequately validated the ------(b)(4)----- assay portion of their potency assay. In addition, the SOPs, instrument qualification, reagent qualification, and quality controls of the assay are adequate to ensure consistent performance of this assay as part of manufacturing. The ------(b)(4)----- laboratory has adequate procedures for instrument quality control, instrument validation, installation and training of staff.

RELEASE TO INVENTORY, SHIPPING, AND PREPARATION INSTRUCTIONS

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

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Cord blood Selection

The entire inventory is listed with The National Marrow Donor Program (NMDP) Registry, the Caitlin Raymond International Registry and the Bone Marrow Donor Worldwide Registry. Unlicensed units will be distributed under NMDP IND ((b)(4)).

When a lot of HPC, Cord Blood is identified and requested for release, confirmatory HLA and molecular virology must be performed either by the applicant or the transplant center that request the unit. The applicant will ship a segment to the transplant center if the confirmatory test is performed by transplant center. Screening result for hemoglobinopathy must be obtained. A cryopreserved vial containing a sample of the final product post processing will be thawed to determine TNC recovery and viability (see Retention Samples section for a description of the samples stored for testing and retention samples). All test results are reviewed by the Lab Director, Medical Director, and the quality unit. If the post thaw (of the vial) viability and TNC recovery is below the acceptance criteria, the product will be released only under the NMDP IND.

The applicant will obtain written request from a recipient's physician or designee. The search coordinator prepares a Summary Release Report that includes a review of all records (processing, HLA, donor infectious disease testing, hemoglobin testing, storage, labeling, and maternal medical history review). The documentation is reviewed by the Director of Regulatory Affairs, followed by a final review by both the Medical Director and Executive Director. The applicant will make an attempt to contact the mother to obtain the baby's health status. Any medical conditions that may contradict the transplant will be evaluated by the medical director. The final release is signed off by both the quality unit and the medical director. The release report, receipt instructions, thawing instructions, and other labeling material will be shipped along with the HPC, Cord Blood to the transplant center.

Reviewer's Comment:
The selection procedure is acceptable.

Shipping to Transplant Center:

-------(b)(4)------- handles all domestic shipments. The courier picks up HPC, Cord Blood Monday through Thursday and delivers by 9:00 AM the next day. Same day shipment can be arranged if requested by the transplant center. -----(b)(4)------ handles all international shipments. -------(b)(4)---- picks up HPC, Cord Blood on Monday through Friday and weekend if necessary. (b)(4) courier services are trained to handle dry shippers charged with liquid nitrogen and the importance of prompt delivery of HPC, Cord Blood. ClinImmune Labs staff track the shipping and receiving documentations, and the tracking information is also provided to the transplant center.

The applicant charges and labels the dry shipper 24 hours before the shipment. The temperature recording log is activated before the HPC, Cord Blood is placed to the shipper. Two lab members check the identifications and necessary documentations.

Shipping-dry shipper validation

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

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Note: *The FDA recommended minimum temperature for HPC, Cord Blood storage and shipping is -150^{o}C, which is the temperature of the liquid nitrogen vapor phase. ClinImmune validated the shippers at the (b)(4), lower than recommended, to show that these shippers can maintain -150^{o}C or lower during shipping.*

Reviewer Comment:
This validation is acceptable.

Receipt and Storage Instructions:

The staff at the transplant center verifies the identity of the HPC, Cord Blood and accompanying records, the integrity of the shipper and the HPC, Cord Blood container, and the temperature of the shipper. The HPC, Cord Blood must be stored at ≤ -150°C prior to transplantation. If the container is failed and the product is thawed at the time of arrival, instructions are to notify the ClinImmune Labs, UCCBB immediately.

Thawing and Emergency Recovery Instructions

The applicant will provide the detailed thawing and emergency recovery instructions with the package insert, which will be shipped to the transplant center along with the CBU. The thawing process consists of three steps 1) thawing; 2) reconstitution (dilution); and 3) washing (removal of cryoprotectant)/resuspension. The instructions provided in the PI will include procedures for both options of thaw and reconstitute and thaw, wash, and reconstitute. The recommended thawing solution is 5% human albumin in 10% Dextran 40.

Reviewer Comment:
The handling and thawing instructions and emergency recovery procedure are adequate.

Thawing and Cryoprotectant Removal Validation

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***Reviewer Assessment of Thawing Validation**:*
This validation is acceptable.

The applicant validated Thaw/Infuse, Thaw/Dilute, and Thaw/Wash methods. However, the applicant only includes Thaw/Dilute and Thaw/Wash in the thawing instruction section of the package insert.

The data provided supports four (4) hours shelf life post thaw.

RETENTION SAMPLES

The applicant reserves multiple samples for future testing or for sample retention.

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PRODUCT STABILITY AND EXPIRATION DATING:

The applicant performed a stability study and the information below was submitted with amendment 4.

The applicant randomly selected (b)(4) CBUs that were processed -(b)(4)- in 2005 and (b)(4) CBUs that were processed ------------(b)(4)----------------- in 2007.

Acceptance criteria:
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(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)

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

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In this validation, the HPC, Cord Blood that were manufactured ---(b)(4)--- were produced in 2005 and the ones that were manufactured -----(b)(4)----- were produced in 2007. The expiration dating should not be different between the two processing methods, therefore the reviewer concludes that the shelf life of the CBUs is 5 years, the time between the implementation of the ---(b)(4)--- method and the stability study was performed.

----------*(b)(4)*----------
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CONTROL OF ASEPTIC PROCESSING

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

COMPUTER SYSTEMS AND VALIDATION

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

LABELING AND TRACKING

Donor Tracking and Labeling:

A unique identification number is assigned sequentially by the Cord Blood Bank Manager (CBBM) database system. The identification number (ID #) starting with "8" (e.g. 8xxxxxx) is

assigned to the cord blood unit. A corresponding ID# starting with "7" (e.g. 7xxxxxx) is assigned to the birth mother. Pre-printed barcode labels are included in each collection kit packet. At the time of donor screening and collection of the cord blood unit, a barcode label is placed on the consent forms, family medical history and maternal risk questionnaires, labor and delivery forms, the collection bag and all other associated forms and tracking lists. All maternal blood specimens are labeled with the barcode ID # assigned to the birth mother.

To maintain linkage between the birth mother and the infant donor, a barcode label with the cord unit ID# is placed on the Maternal Demographic form that is completed by the birth mother. The unit ID# is also included 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 donor identification number allows tracking from the donor to the recipient and vice versa.

Furthermore, the applicant uses the ISBT 128 data structure for the donor identification number that is included on the cord blood collection bag and the final cryopreserved HPC, Cord Blood container labels. The ISBT 128 number includes the cord blood unit ID # that is assigned by the CBBM database without the first digit "8".

Example: CBBM assigned #: 8111111
ISBT ID: W3333 12 111111 (Facility ID# + Year + serialized ID#)

The ISBT 128 donor identification number is also listed on the cord blood unit report that is provided to the transplant center.

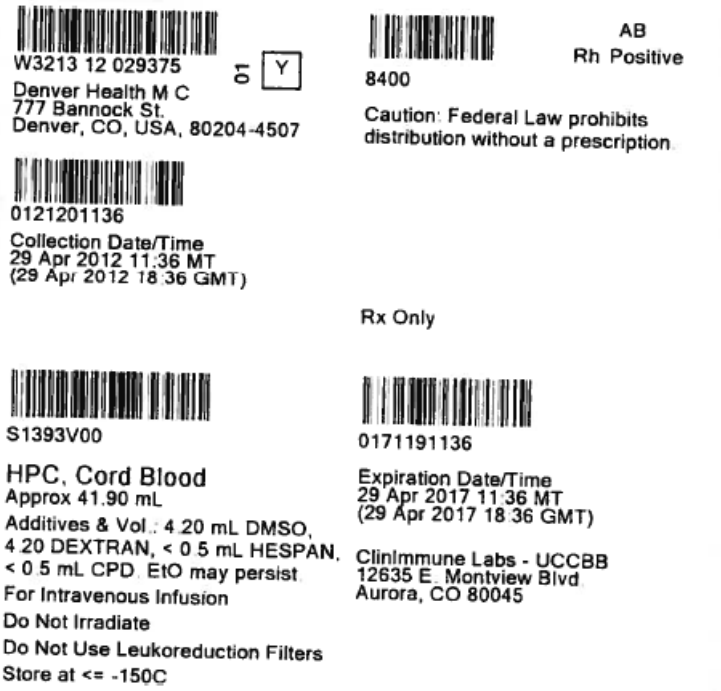
Reviewer comment:
The described tracking method is acceptable.

Container and Package Labels

Container:
The product container for HPC, Cord Blood is the cryobag. The label is affixed before cryopreservation when final disposition of the lot is not known, therefore the affixed label does not include all of the information required for a full container label, and is thus a partial label.

A sample of the label to be affixed to the cryobag and the metal canister is shown in Figure 4.

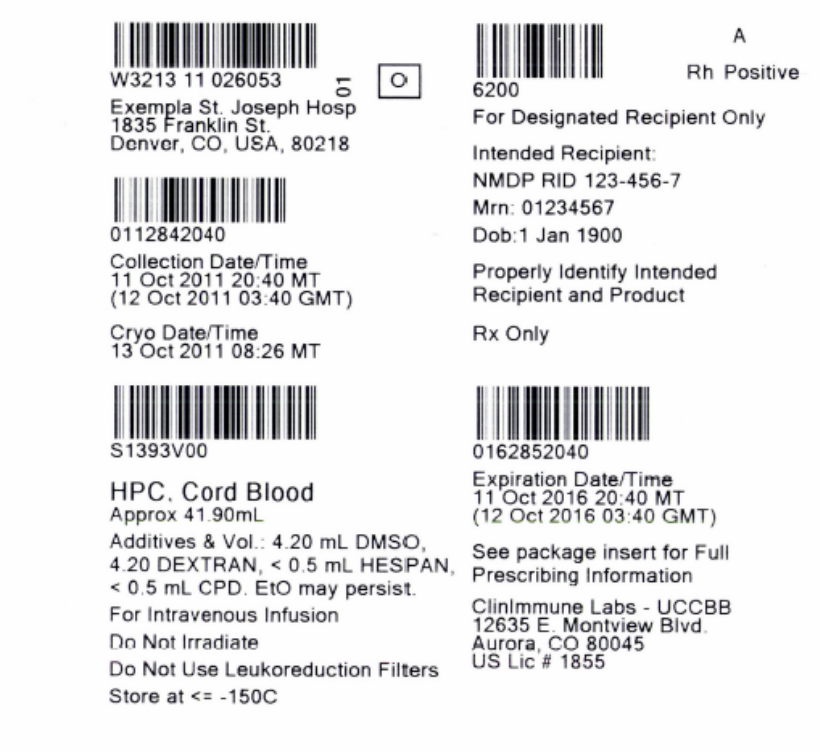
Figure 4: Container Label



Package

The package label for HPC, Cord Blood will be placed inside the metal canister that holds the cryo bag, prior to shipping. A sample of the package label is shown in Figure 5.

Figure 5: Package label



Reviewer comment:
The container and package labels were reviewed in collaboration with APLB. The applicant revised the labels according to our recommendations to meet the requirements in the regulations.