MEMORANDUM

BLA 125432
CMC Review of Original Submission

HPC, Cord Blood

LifeSouth Community Blood Center Inc.

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

Reviewed by:		**Signature**
Mohammad Heidaran, Ph.D.	**Review Committee Chairperson -Other sections including process validation, freeze, thaw and wash validation, emergency recovery, shipping, stability, labeling, container closure and reserve samples**	
Eric Dollins, Ph.D.	**Assay Validation**	
Joydeep Ghosh, Ph.D.	**Sterility Validation**	
Fatima Abbasi, M.S.	**Flow Cytometry Validation**	
Karoll Cortez, M.D. **Safa Karandish, B.S., M.T.**	**Donor Eligibility and Collection**	
Concurred by:		
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EXECUTIVE SUMMARY

Action Due Date: June 17, 2013

Recommendation:

We recommend approval of BLA 125432. The approval should be granted for HPC, Cord Blood lots manufactured after the approval date.

Product Overview:

Hematopoietic progenitor cells, cord blood (HPC, Cord Blood) is manufactured by the LifeSouth Community Blood Center Inc. located at Newberry Road Gainesville, FL. Manufacturing and product quality standards for HPC, Cord Blood manufactured at LifeSouth 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 -------(b)(4)------- automated system. The final hematopoietic progenitor cells, Cord Blood product consists of a 25 ml frozen product cryopreserved in 10% DMSO and 1% Dextran 40 using a controlled rate freezing process ---(b)(4)--- and then stored in liquid nitrogen (b)(4). Approximately (b)(4) Hetastarch remains from cord blood processing. HPC, Cord Blood is cryopreserved in two-compartment freezing bags. The larger compartment contains 80% (20 ml) of the suspension, and the smaller compartment contains 20% (5 ml). The HPC, Cord Blood is placed and maintained inside a protective metal canister. The steel canisters are labeled and enclosed in a plastic foam thermal sleeve. Each unit is frozen. HPC, Cord Blood is shipped frozen in special shipping containers (Dry-Shippers) designed to maintain a controlled environment and a very low temperature ($\leq$ -150^{o}C). The temperature is electronically monitored and recorded during the entire transit time. The final product is tested for purity, identity, sterility, and potency.

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

Proprietary Name: None

Non-proprietary Name: Hematopoietic progenitor cells, Cord Blood (HPC, Cord Blood)

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

Inactive Ingredients:	**UNII Code:**
Dextran 40	K3R6ZDH4DU
DIMETHYL SULFOXIDE	YOW8V9698H
Hetastarch	875Y4127E

Therapeutic and Pharmacological Class: Allogeneic cord blood hematopietic progenitor cells therapy

Dosage Form: Injectable Suspension

NDC #: None (ISBT-128 compliant)

Review Findings:

A team of 5 reviewers evaluated the CMC information. This review is a compilation of all the CMC reviews. During the initial CMC review, several deficiencies were identified. These issues were communicated to the applicant via letter comments and teleconferences dated July 16 and 31, and October 2, 2012. At the time of mid-cycle meeting on October 18, 2012, a list of major outstanding questions were identified and communicated to the applicant in form of several information requests dated October 24, November 8 and 28, December 13 and 18 of 2012 and January 30, 2013. LifeSouth's responses to the question are detailed in amendments dated 11/13/2012, 12/6/2012, 12/19/2013, 1/30/2013, 3/8/2013 and 5/16/2013 and telecon summary dated October 2, 18, 24, November 8, February 26, March 15 and 27 and April 26. The applicant's response and each reviewer's assessments are summarized in the body of the text. All outstanding issues have been adequately satisfied.

Pre-license inspection:

A pre-licensure inspection was conducted September 24-28, 2012, during which the facility was issued a form 483 citation. The major observations were related to the batch record, quality control procedures, labeling, aseptic process validation and training, clean room environment, written procedures for initiating investigation for complaints, adverse events and OOS, and incomplete SOPs or SOPs not followed. LifeSouth provided their response in a letter dated October 19, 2012 and an amendment to the file received December 7, 2012.

SUMMARY OF APPLICATION

History of LifeSouth: The following history was provided by the applicant. LifeSouth's cord blood bank (LifeCord) was established in 1997 by collaborative agreement between three entities: the University of Florida (UF) faculty of the Department of Medicine, Shands at UF (the teaching hospital for the University of Florida) (Shands), and LifeSouth Community Blood Centers, Inc. LifeSouth's cord blood bank has operated under IND BB-7520, approved by the UF IRB to collect, process, bank, and distribute cord blood units for transplantation since that time. Initially, cord blood units were collected from mothers delivering only at Shands and North Florida Regional Medical Center, both in Gainesville, Florida. In 2002, four hospitals in southeastern Alabama (Montgomery and Opelika) obtained IRB approval for the research initiative to collect cord blood units in that state. In 2010, Northeast Georgia Medical Center in Gainesville, GA, also began collections under individual hospital and/or UF IRB-approval. Henry Medical Center in Atlanta, GA, began collections in December 2011. Initially accredited by FACT-NetCord for cord blood banking in 2007, the cord blood bank continues to be FACT- NetCord accredited.

In the 14 years of its existence, LifeCord has collected more than –(b)(4)-- cord blood units, of which --(b)(4)--met all criteria for banking and are stored and listed for transplant in the NMDP registry as of October 19, 2011. ---(b)(4)----- units have been distributed for transplant into 81 patients needing hematopoietic reconstitution for malignancy and other diseases. Data from 77 of these transplants have been reported back to the LifeCord program through the CIBMTR and NMDP as of October 31, 2011. In March 2011, the LifeSouth Board of Directors authorized creation of a consolidated manufacturing site in the LifeSouth Headquarters facility on Newberry Road in Gainesville, FL. The facility renovation commenced in June 2011 to create receiving, storage, laboratory and clean room capabilities which were occupied after certification for occupancy in October 2011. New automated and robotic equipment were purchased and installed, beginning in September 2011. Nearly all processing and testing activities have been relocated to this site where manufacturing began in October 2011.

PRODUCT RELEASE SUMMARY (Overview of Manufacturing Process):

This application is a request for licensure of those cord blood units manufactured and banked beginning in March 2012 in the site on Newberry Road, Gainesville, FL. We recommend granting licensure for units manufactured after the approval date. The basis of this decision is that HPC, Cord Blood manufactured prior to this date have not been demonstrated to be fully compliant with CGMPs.

HPC, Cord Blood will be manufactured to ensure safety, purity, potency, and identity of the product as shown in the following table:

Table 1: Product Release Specification

Product Characteristics	Testing Required	Tests Performed	Sample (Type and Timing)	Results of Product Testing
Safety	Infectious diseases	HBsAg anti-Hep B core Anti-HCV Anti-HIV-1/2 HTLV-I/II T. cruzi CMV Syphilis HIV RNA / HCV RNA / HBV DNA WNV RNA	Maternal peripheral blood obtained within 7 days of cord blood collection	All tests negative except non-treponemal test for Syphilis when confirmatory test is negative. (Cytomegalovirus (CMV) results are recorded).
	Sterility - Bacterial and fungal cultures	---------- ----(b)(4)------- ---------- ----------	HPC, Cord Blood	No growth
	Hemoglobin	---------- ----(b)(4)------ ----------	---------- -----(b)(4)------ -----	No homozygous hemoglobinopathy

Product Characteristics	Testing Required	Tests Performed	Sample (Type and Timing)	Results of Product Testing
		------(b)(4)--------- Performed by contract laboratory: (b)(4)		
Purity and Potency	Total nucleated cells (TNC)	-----(b)(4)-------- -------	HPC, Cord Blood	≥ 5.0 x 10^8 TNC / unit HPC, Cord Blood
	Viable nucleated cells	---------- ----(b)(4)---------- ----------	HPC, Cord Blood	≥ 85% viable nucleated cells
	Viable CD34+ cells (flow cytometry)	---------- -----(b)(4)---------- ----------	HPC, Cord Blood	≥ 1.25 x 10^6 viable CD34+ cells / unit HPC, Cord Blood
	----(b)(4)---------- -------	---------- -----(b)(4)---- ---------- ---------- --------	----(b)(4)------	----(b)(4)--------
Identity	Human leukocyte antigen (HLA) Typing	---------- --(b)(4)----- ---------- ---------- Performed by contract laboratory: (b)(4)	Cord blood ------- ---(b)(4)-- ---------	Report
	Confirmatory HLA typing	---------- --(b)(4)----- ---------- ---------- ---------- ---(b)(4)---------- ---------- --- Performed by contract laboratory: (b)(4)	From CBU segment From CBU segment	Confirms initial typing Confirms initial typing
	At collection, Maternal / CBU ID on collection bag and collection form At shipment, Steel Canister and CB Bag ID labels	Verified by staff and recorded on CBU records	N/A	Labels must match
	Blood group and Rh type	ABO/Rh type	Pre-processing & post-processing samples	ABO types must match

Cord blood units are obtained at eight collection sites in three states, manufactured in one receiving and processing location, tested in multiple laboratories, and maintained in a single, final storage facility in Gainesville, FL. Three contract laboratories are used: HLA typing in ----(b)(4)----------, Infectious Disease screening in ----------(b)(4)----------, and hemoglobinopathy testing in ----------(b)(4)---------- All laboratories are CLIA-certified to provide the testing services required.

Contamination precautions include handling the cord blood units in a certified -(b)(4)- clean room dedicated solely to cord blood manufacturing. No other biologic material is processed within the dedicated space. ----------(b)(4)----------.

Processing is done using an automated method ---(b)(4)-- in single-use, sterile, closed-system kits --(b)(4)--. All attachments to the CBU for sampling and for connecting the single-use kit are done using validated sterile connecting devices. Separated samples are passed back through the original pass-through window for immediate testing in the adjacent laboratory or placed into appropriate storage for send-out testing. Chemicals are added to the CBU via a filtered port using a single-use, sterile syringe within a biologic safety cabinet. Procedures are validated and personnel are trained for response to unexpected CBU breakage resulting in splashes or spills. After processing, each CBU is passed through a second pass-through window into the adjacent freezing and storage area where final labeling, overwrap application, and controlled-rate freezing are done using an automated instrument -------(b)(4)-------. All data related to cryopreservation and storage are captured electronically.

FDA approved container and closure systems used for cord blood collection, processing, and storage are used. These include ----------(b)(4)----------.

Infectious disease testing is performed by ----------(b)(4)----------, a laboratory that is CLIA-certified and licensed by the State of Florida to provide such testing. FDA approved, licensed, or cleared test kits and reagents are utilized.

Other testing methods include the use of --------(b)(4)----- for sterility, -----(b)(4)--------- for hemoglobin testing, TNC counts using -----(b)(4)----------, nucleated cell viability assay using --------(b)(4)-------, CD34+ viability using --(b)(4)--- flow cytometry, HLA typing, ABO blood group and Rh type, colony-forming unit (b)(4) assays using ---------(b)(4)---------- and nucleated red blood cell counts using --------(b)(4)---------. This information was reviewed in the Testing and Method Validation section under “Other test methods”.

The methods of manufacturing and related SOPS and validations studies (including aseptic process validation) covering all critical processing steps, including donor selection, collection, transport from collection to processing facility, processing, storage, and shipping and handling, have been included in the review.

CHEMISTRY, MANUFACTURING, AND CONTROLS

Manufacturing and controls information

HPC, Cord Blood Description and Characterization

Product characterization tests required for safety includes infectious disease testing, sterility as determined by lack of growth for both bacterial and fungal cultures, and hemoglobinopathy testing. For purity and potency, LifeSouth intends to test for Total Nucleated Cells (TNC), Viable nucleated cells and viable CD34+ cells. For identity, LifeSouth performs HLA typing, confirmatory HLA typing, blood group/ABO and Rh typing.

Manufacturer(s)

Identification

Cord blood manufacturing and all administrative functions occur at the Corporate Headquarters of LifeSouth Community Blood Centers (LifeSouth Blood Bank Inc.) located at 4039 Newberry Road Gainesville, Florida 32607 with FDA Registration #: 3003707120.

Collection sites

LifeCord, the cord blood program of LifeSouth, collects cord blood units at eight collection sites. Sites are located in Florida, Georgia, and Alabama in hospitals that LifeSouth supplies with blood components. For cord blood units collected in Florida, at least once per day, a LifeSouth ground courier transports the collected units directly to the processing facility at LifeSouth Corporate Headquarters in Gainesville, Florida. In Alabama and Georgia, a LifeSouth courier transports collected cord blood units from the collection hospital to the LifeSouth regional location affiliated with that hospital. After delivery to the region, the CBUs are sent by air (via LifeSouth's contract plane) and ground courier to LifeSouth Headquarters in Gainesville, Florida, arriving around (b)(4) each day. Processing occurs in Gainesville, Florida. A list of all collection sites is included in table below:

Table 2: Collection Sites

LifeSouth location	Supported Collection Hospitals
LifeSouth Corporate Headquarters 4039 Newberry Road Gainesville Florida (352) 224-1600	***North Florida Regional Medical Center*** *Collecting since*: 1997 6500 Newberry Road, Gainesville, FL 352-333-4000 ***Shands at the University of Florida*** *Collecting since*: 1997 1600 SW Archer Road, Gainesville, FL 352-265-8000

LifeSouth location	Supported Collection Hospitals
LifeSouth Northeast Georgia Region 1200 McEver Road Extension Gainesville, GA 30504 770-538-0500	***Northeast Georgia Medical Center*** *Collecting since*: 2010 743 Spring Street, Gainesville, GA 770-219-9000
LifeSouth Southern Crescent Region 329 Westridge Parkway McDonough, GA 30253 678-432-0637	***Henry Medical Center*** *Collecting since*: 2011 1133 Eagle's Landing Parkway, Stockbridge, GA 30281 1-888-795-2707 x61352
LifeSouth Montgomery Region 139 Carmichael Road Montgomery, AL 36106 334-260-0803	***Baptist Medical Center South*** *Collecting since*: 2002 2105 East South Blvd., Montgomery, AL 334-288-2100 ***Baptist Medical Center East*** *Collecting since*: 2002 400 Taylor Road, Montgomery, AL 334-277-8330 ***Jackson Hospital*** *Collecting since*: 2002 1725 Pine St., Montgomery, AL 3610 334-293-8000
LifeSouth East Alabama Region 505 East Thomason Circle Opelika, AL 36801 334-705-0884	***East Alabama Medical Center*** *Collecting since*: 2002 2000 Pepperell Parkway, Opelika, AL 334-749-3411

Contract Laboratories

HLA typing, hemoglobinopathies, and maternal testing (infectious disease and maternal ABO/Rh) are performed by contract laboratories. The table below summarizes the tests performed and facility information including FDA registration, CLIA certifications, and accrediting organizations. LifeSouth has provided copies of the relevant certificate(s).

Table 3: Contract Laboratories

Performs	Facility Information
HLA typing	---------- ----------(b)(4)---------- ---------- ---------- ----------(b)(4)---------- ---------- ----------

Performs	Facility Information
	----------(b)(4)---------- ----------(b)(4)---------- ----------: ----------(b)(4)---------- ----------
Hemoglobinopathy testing	---------- ----------(b)(4)---------- ---------- ---------- ----------(b)(4)----------
Maternal Testing: Infectious Disease ABO/RH	---------- ----------(b)(4)---------- ---------- ---------- ----------(b)(4)----------

Reviewer's comment*: LifeSouth's SOP for qualification of contract vendors or suppliers was reviewed during the PLI (SOP QA.4.1, revision Dec2011) and found acceptable. The SOP is designed to ensure that acquired supplies, services, and equipment conform to specified requirements using a controlled process.*

CORD BLOOD COLLECTION

LifeSouth collects cord blood units at eight hospitals in three States: Florida, Georgia, and Alabama. Collection sites in Georgia and Alabama are affiliated with regional LifeSouth facilities. A list of LifeSouth regional facilities and the affiliated collection sites is included in the table above.

At each LifeSouth regional facility, there are dedicated cord blood program staffs (referred to as Cellular Therapy Staff), who are responsible for the following:

- Maintaining collection supplies at each hospital
- Educate birth mothers on cord blood donation, provide educational brochure and obtain written permission to collect cord blood
- Train physicians/midwives and labor and delivery staff on cord blood collection
- Serve as liaison to the collection hospital staff for all cord blood collection related activities.

At each collection hospital, labor and delivery nurses pre-screen the birth mothers and assist in the collection of cord blood. Trained physicians/midwives are responsible for performing the collection procedure.

Birth mothers interested in donating their baby's cord blood are asked to complete and sign the Permission for Cord Blood Collection form in advance but before going into active labor. The permission for cord blood collection is not considered as the full donor consent but it serves as the notification to the labor and the delivery staff of the mother's interest in cord blood donation. The birth mothers are pre-screened by the labor and delivery nursing staff and potential donors with any of the following findings are excluded and the cord blood is not collected:

- Mother has positive test results for HIV, HCV, or HBV
- Mother age < 18years
- Stillborn infant
- Mother is a surrogate; infant resulted from donated egg, sperm or embryo
- Mother has evidence of illicit needle use
- At the time of delivery; pus, significant placental tears, or sign of infection
- Malodorous placenta or amniotic fluid, or suspicion of chorioamnionitis
- Placental trauma at delivery
- Excessive maternal bleeding in labor
- Transfusion or infusion of >2 liters of fluid during labor & delivery.
- Evidence of active genital herpes for vaginal deliveries
- Evidence of significant genital human papilloma virus (HPV) infection for vaginal deliveries
- Multiple births
- Gestational age < 34 weeks
- Fetal malformations including metabolic disorders, chromosomal abnormalities or structural anomalies
- Mothers receiving antibiotics

The cord blood collections are performed in-utero immediately after normal vaginal or c-section deliveries. After delivery, the LifeSouth cord blood program staff meets in-person with the birth mother to obtain full signed consent, complete donor and family medical history interview and to obtain a signed request to get access to her medical records from the hospital.

Reviewer comment: *The SOP CB.2.2: Obtain Mother's Consent, Medical History, and Medical Records that was submitted in the original BLA stated that the full consent is obtained after it has been determined whether the unit is "bankable"; however, the SOP did not define the criteria for bankable units. Also, it was not clear how the LifeSouth cord blood program staff responsible for obtaining the full consent at the delivery hospitals get the information regarding the bankability of a unit from the processing laboratory. In the teleconference dated 10/2/2012, the applicant was asked to submit the revised SOP and provide further clarification regarding the consent process. In the amendment dated 11/13/2012, LifeSouth explained that the criteria for bankability of units after collection is defined in the reference document entitled CBU weight and TNC level Requirements. The processing laboratory staff determines the CBU weigh and TNC when the unit is received in the laboratory. If the unit meets the minimum requirements*

(refer to the Initial Cord Blood Qualification Criteria section), then the information is sent to the staff at the hospital to obtain the full consent. LifeSouth further explained that the infectious disease testing is not performed until after the full consent is obtained. LifeSouth submitted the revised SOP CB.2.2 on 11/13/2012. The response and the revised SOP are acceptable.

Collection Training

The training program is conducted by the certified LifeSouth cord blood bank program staff.

Physicians/midwives attend a collection training session which includes watching a training video, review of SOPs related to aseptic collection of cord blood, labeling and donor assessment. Following the initial training, the first unit collected by each physician/midwife is tested for sterility. If the sterility is negative, the collector is considered trained. The physician/midwife is retrained if the initial sterility result of the first collected unit is positive. Collectors are assessed on --(b)(4)-- basis and results of the sterility testing are provided to each individual collector. If issues are detected with this monitoring collectors are retrained. The LifeSouth training staff also provides ----(b)(4)--- training and updates for the physician/midwives.

The Labor and Delivery nursing are trained on donor pre-screening, assisting the physician/midwives with cord blood collection, labeling and preparing collected units for transportation. On a -----(b)(4)---- basis, the LifeSouth training staff participates in nursing staff meetings to provide updates and answer questions.

LifeSouth maintains the training documentation. The applicant has provided a copy of the slides presented at the training sessions for the physician/midwives and the nursing staff.

Reviewer comment**: The training is acceptable**.

Collection Controls

LifeSouth has established the following controls for the collection procedure:

1. Pre-assembled cord blood collection kits are stored in a temperature controlled storage area at the collection hospital. Each collection kit has an assigned lot # and expiration date. Collection kits contain the following:
    - a PVP ---(b)(4)--- Scrub
    - Clamp or small clip,
    - Underpad (chux),
    - Resealable plastic bag,
    - Collection Form, labels, Donor Identification Number (DIN) stickers and tubes for collection of maternal specimens.
    - Single use collection bag ----------(b)(4)----------
2. For vaginal deliveries, collection is performed in the labor and delivery rooms. For c-section deliveries, collection is performed in the sterile field in the operating room.
3. To minimize risk of contamination, cross contamination or mix-up:
    - Collection staff wears appropriate gowning and protective equipment

- Single use, sterile collection bag and antiseptic swabs are used for collections
- Placenta is checked for pus, significant placental tears, or sign of infection
- The venipuncture site on the cord is disinfected with PVP --(b)(4)--- Scrub
- Collected unit and the CBU Collection form is labeled with the hospital generated maternal label
- Identity of the birth mother on the hospital label is verified against mother's hospital armband.
- Collection staff identity, collection kit lot# and expiration date, collection date and time are documented on the CBU Collection form.
- The collection bag is placed in a single used re-sealable plastic bag.

Storage at Collection Hospitals

Prior to the collection of cord blood, the pre-assembled collection kits are stored in designated areas that are monitored by a Min/Max thermometer. The acceptable temperature range is ----------(b)(4)--------. The temperate range is monitored (b)(4) and documented on the (b)(4) Temperature Record form (CB.2.4). If there is a temperature excursion, the unused kits are marked as quarantine and it is determined whether the kit components are affected by the temperature excursions. Any affected component is replaced and the kit is returned to the inventory for use.

Reviewer comment: *The SOP submitted in the original BLA did not describe the criteria used for determining the affect on the kit components in the event of temperature excursions. In the amendment dated 11/13/2012, LifeSouth submitted the revised SOP CB.2.4: Monitor Collection Kit Storage and CBU Refrigerator Temperatures. The acceptable temperature ranges for each kit component was added to the troubleshooting table. The revised SOP describes that in the event of any temperature excursion, a Reportable Event Form is completed and the event is investigated by the Quality Assurance (QA) department to determine whether any of the components of the pre-assembled collection kits needs to be discarded. The revised SOP is acceptable.*

The collected unit, the completed CBU Collection form, the Permission to Collect form, four hospital generated maternal labels, and the maternal specimens (if collected at time delivery) is placed in a large re-sealable plastic bag. The collected units are stored in a secure, temperature-controlled, designated area or refrigerator that is monitored by a Min/Max thermometer on (b)(4) basis. The acceptable temperature range is ---(b)(4)----------. The temperate range is monitored (b)(4) and documented on the (b)(4) Temperature Record form (CB.2.4). Temperature excursion events, before or after collection of cord blood, is documented on a Reportable Event form. The Cellular Therapy Manager determines the proper disposition of the unit and documents the corrective action.

Reviewer comment: *LifeSouth was asked to provide information regarding the designated storage area for the collected units at the hospitals and the process for investigating temperature excursions during storage. In the amendment dated 11/13/2012, LifeSouth indicated that units are placed in a designated container prior to being placed in the transport box for shipment to the processing facility. The storage container is located on the Labor and Delivery floor of the*

hospital. LifeSouth also provided the revised SOP CB.2.4. The revised SOP includes troubleshooting instructions and explains that the temperature excursion events are investigated by the QA department to determine the acceptability of the units. The response and the revised SOP are acceptable.

Transportation From Hospitals to the Processing Facility

For transportation of units, a maximum of (b)(4) collected units are placed in an insulated transport box containing (b)(4) gelpacks. Cold (b)(4) gelpacks are used for transportation of units during Summer and room temperature gelpacks during Winter. A unit pick-up log is completed and a DIN (donor identification number) sticker obtained from the collection kit is placed on the log.

LifeSouth has established agreements with designated couriers for transportation of cord blood units to the processing facility, on daily basis at pre-scheduled pick-up times.

For cord blood units collected in Florida, at least once per day, a LifeSouth ground courier transports the collected units directly to the processing facility. For units collected at the hospitals in Alabama and Georgia, a LifeSouth courier transports the units from the collection hospital to the affiliated LifeSouth regional location. The transport boxes are unpacked and the units are stored in designated refrigerators at the regional facility. The units are then repacked in the transportation box following the procedure described above. The units are shipped by air (via LifeSouth's contract plane) from the regional facilities to LifeSouth headquarters in Gainesville, Florida, arriving around (b)(4) each day.

Reviewer comment: *The applicant was asked to describe how they ensure that the units are maintained within acceptable temperature range during transit. In amendment dated 11/13/2013, the applicant submitted a validation report for the transport boxes. Refer to the transport validation section.*

Initial Cord Blood Qualification Criteria

When the unit is received by the processing laboratory, the following initial qualification is performed (CB.7.1.2):

1. Verification of the DIN number on the cord blood unit collection bag matches the DIN number on the collection form.
2. Visual inspection of the cord blood container for clots
3. Pre-processing weight determination
4. Pre-processing TNC: ---(b)(4)----- (for Caucasian donors) and ---(b)(4)--- (for minority donors)

Reviewer comment*: LifeSouth was asked to clarify whether the DIN is assigned at the hospital or after the unit is received in the processing laboratory. They were also asked to define the acceptable minimum weight of the collected units in SOP CB7.1.2. In the amendment dated 11/13/2012, LifeSouth submitted SOP CB.4.1: Prepare Collection Kits and Sample Tube Set and*

confirmed that the DIN stickers are included in the pre-assembled collection kits and are placed on the collection bag and the collection form at the hospital. In the amendment dated 12/19/2012, LifeSouth submitted the revised SOP CB.7.1.2 which included the minimum acceptable weight. The revised SOPs are acceptable.

COLLECTION VALIDATION

In the BLA summary (volume A, section 2.2.2.1(a)(i)), LifeSouth described that the validation of the collection procedure is conducted at each collection site as part of the initial site qualification. After the collectors are trained, total of (b)(4) collected units are evaluated. As an example, LifeSouth has submitted the validation protocol (dated December 2010) and the report for the North East Georgia collection site.

Validation protocol:

(b)(4) cord blood units were collected by trained physician/midwives and nursing staff following the established collection, labeling, donor pre-screening and transportation procedures.

Evaluation & Acceptability criteria:

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

Reviewer comment: *In the filing letter, LifeSouth was asked to provide additional information regarding the validation acceptability criteria and the number of units evaluated for the validation. Also clarification was requested regarding the reference to (b)(4) collection bags in the validation plan. In the response letter submitted on 8/24/2012, LifeSouth explained the following:*

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

The responses were acceptable.

Validation results

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

The validation report also states that some minor issues were noted with documentation and packing but they were all satisfactorily corrected through follow-up with staff.

Reviewer comment*: The validation summary report that was submitted initially was incomplete. In the amendment dated 11/13/2012, LifeSouth explained that in the original BLA, the summary page that included some of the validation results was mistakenly excluded. The complete validation report was submitted on 11/13/2012. The validation met the acceptance criteria. Furthermore, LifeSouth discards units that do not meet the banking acceptability criteria.*

DONOR ELIGIBILITY

The donor eligibility procedures include screening and testing of the cord blood donors for risks of communicable diseases or disease agents. Prior to the collection of cord blood, birth mothers are prescreened and excluded from collection based on the criteria listed in the cord blood collection section.

Donor Screening

The donor screening process includes the review of the birth mother's and infant donor medical records and the maternal risk questionnaires to identify risks for relevant communicable disease agents or diseases (RCDAD). The medical records are requested from the hospital and if not received within -(b)(4)-- of the initial request, the LifeSouth staff picks up the records from the hospital. The applicant uses the Cord Blood Maternal Risk Questionnaire and a Family Medical History Questionnaire and the action guides provided by -(b)(4)-. The action guides define the risk factors that would determine donor deferral or ineligibility.

Donors are screened for risk factors associated with HIV 1/2, HBV, HCV, Syphilis, HTLV 1/2, WNV, Sepsis, Vaccinia, TSE (CJD/vCJD), and xenotransplantation. In addition, donors are screened for -----(b)(4)---------- and ---(b)(4)-------- which are not currently required by the FDA.

Reviewer comment: *In the SOPs submitted in the initial application, LifeSouth did not clearly define the clinical and physical evidence and risk factors for RCDADs for which the donors are*

screened. In the amendment dated 1/30/2013, LifeSouth submitted the final SOP CB-MO-1.5: Determine CBU Donor eligibility which addressed all the donor screening deficiencies.

Table 4: Donor Testing

Test	Test	Manufacturer
HBsAG	------(b)(4)----------	------(b)(4)----------
	------(b)(4)----------	------(b)(4)----------
Anti-Hep B core	------(b)(4)----------	------(b)(4)----------
	------(b)(4)----------	------(b)(4)----------
anti-HCV	------(b)(4)----------	------(b)(4)----------
anti-HIV-1/2	------(b)(4)----------	------(b)(4)----------
HTLV-I/II	------(b)(4)----------	------(b)(4)----------
T. cruzi	------(b)(4)----------	------(b)(4)----------
CMV	------(b)(4)----------	------(b)(4)----------
Syphilis	------(b)(4)----------	------(b)(4)----------
HIV RNA / HCV RNA / HBV DNA	------(b)(4)----------	------(b)(4)------
	------(b)(4)----------	------(b)(4)----------
WNV RNA	------(b)(4)----------	------(b)(4)------
	------(b)(4)----------	-----(b)(4)----------

The infectious disease tests are performed at the -----(b)(4)---------- using FDA licensed approved or cleared donor screening test. The contract testing lab is FDA registered and CLIA certified.

Reviewer comment: *LifeSouth was asked to explain the reason for using multiple infectious disease assays. In the amendment dated 11/13/2012, LifeSouth clarified that for some tests, two assays have been listed because (b)(4) may use either assay depending on the availability; however, all the listed assays are FDA licensed, approved or cleared donor screening tests. The applicant also corrected the manufacturer information for the CMV assay (the corrected information is listed in the table above). The response is acceptable.*

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 hospital generated maternal labels which include birth mother's name, medical record # and the date of birth by the collection staff. Cord blood unit is not accepted for banking if the birth mother has received a transfusion of more than --(b)(4)-- of blood, blood components or colloids within (b)(4) or more than ---(b)(4)-- of crystalloids within ---(b)(4)-- before the specimens for infectious disease testing are collected.

Reviewer comment: *The SOPs submitted in the original BLA did not clearly explain the process for assignment of the donor identification number (DIN) to the birth mother and shipment of the collected specimens to the testing laboratory. In the amendment submitted on 11/13/2012, LifeSouth explained that the maternal specimens are transported to LifeSouth headquarters in a separate shipping container. The maternal specimens are then labeled with a maternal DIN (refer to the Cord Blood Donor Tracking section on additional information regarding DIN). To maintain linkage, a maternal DIN sticker is placed on the CBU Collection Form that includes the cord blood unit DIN. The remaining DIN stickers are maintained in the CBU file. The birth mother information, maternal DIN and the cord blood unit DIN are entered into the (b)(4) computer system as additional measure for maintaining linkage. The maternal specimens are then shipped from the headquarters to the (b)(4) laboratory for testing. LifeSouth submitted SOPs CB4.1, CB6.1, CB.5.3 on 11/13/2012. The response is acceptable.*

Final Donor Eligibility Determination

LifeSouth determines the donor to be eligible if the donor screening does not identify any risk factors for RCDADs and all the infectious disease test results are negative or non-reactive (except for CMV). Only HPC, Cord Blood from eligible donors is accepted for licensure.

The LifeSouth Medical Director is responsible for reviewing all the screening and testing results; and making the final donor eligibility (DE) determination. The medical director completes and documents the final DE on the CBU File Review Checklist C: Cord Blood Donor Eligibility before the QA department determines the acceptability of the HPC, Cord Blood for licensure and listing in the registry.

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

Reviewer comment: *The SOP and forms submitted in the original BLA did not clearly define the process for the final donor eligibility determination. In the amendment dated 1/30/2013, LifeSouth submitted SOP CB-MO-1.5: Determine CBU Donor Eligibility, Revised CBU File Review Checklist C: Cord Blood Donor Eligibility and the Certificate of Analysis which addressed all the DE determination deficiencies. The donor eligibility determination is performed in accordance with the regulatory requirements.*

CORD BLOOD PROCESSING, VALIDATION

LifeCord CBUs are processed (volume reduced) in an -(b)(4)-- clean room using the ----------(b)(4)---------- with a UCB-HES (cord blood-hetastarch) protocol. The -(b)(4)- system is an automated CBU processor incorporating a functionally-closed and sterile single use ---(b)(4)-------.

Process Validation

1 page redacted due to (b)(4)

[(b)(4)]

Storage, Validation Summary

LifeSouth uses the -------(b)(4)---------- system for the cryopreservation and storage of the final product. The -------(b)(4)---------- system is an automated, controlled-rate, liquid nitrogen freezer used to freeze and store umbilical cord blood. The -----(b)(4)--------- consists of the following key components: -------(b)(4)----------
---

Briefly, LifeSouth CBUs are first volume reduced using the ---(b)(4)----- processing system. DMSO cryopreservative (---(b)(4)---------) is then added to the processed CBU, and the CBU is frozen and stored using the ----------(b)(4)----------. When a CBU is requested for transplant purposes, the unit is retrieved from the ---(b)(4)--- system and transported to the transplant center via a liquid nitrogen dry shipping container. Upon arrival at the transplant center, the CBU is thawed and prepared for transplant. Validated procedures for thawing and washing are sent with each CBU to the transplant center.

FREEZE, THAW AND WASH VALIDATION

The Freeze, Thaw validation report dated April 2012 contains information related to the validation of cryopreservation, thawing of the product and quality of the product post thaw (see Table 6 below). Three units were tested, and all met the predetermined acceptance criteria for post thaw CD34+ % viability and recovery. However, the firm did not include detailed information about the acceptance criteria for the freezing curve.

[(b)(4)]

***Reviewer comment**: Cryopreservation of the processed cord blood units is performed using the --------(b)(4)----------. LifeSouth was asked to provide detailed validation study results including a freezing curve demonstrating that the final product cryopreservation can be performed reproducibly as intended.*

LifeSouth Response:

LifeSouth provided a detailed summary for validation of cryopreservation of cord blood units using the ----------(b)(4)---------- (attachment A of an amendment received 12/06/2012). The acceptance criteria for the freezing curve were also included in the new validation protocol. These results demonstrated that the freeze and thaw can be performed reproducibly and consistently without significantly affecting cell viability. The LifeSouth response is acceptable.

In regard to the validation study related to the CBUs thaw and washing, the firm has defined a predetermined acceptance criteria for the expected post thaw results for TNC, CD34+ % viability, DMSO content, bag integrity, and sterility. The acceptance criteria for TNC is ----------(b)(4)----------, CD34+ % viability of ----------(b)(4)----------. The results obtained for ----------(b)(4)----------.

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

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

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

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

[(b)(4)]

For bag integrity, LifeSouth monitored the following parameters following the thaw/wash step:
1) ----------(b)(4)----------. The results indicate that all units met the predetermined acceptance criteria except that for 3 out of (b)(4) units the label did not remain on canister.

Reviewer comment*: In regard to the integrity of CBU storage bags, 3 out of* (b)(4) *units the label on canister came off. However for these bags the label on the container remained intact. LifeSouth was asked to provide their plan to implement the corrective and preventive actions addressing this issue.*

LifeSouth Response:

LifeSouth stated that as part of their investigation they have examined an additional (b)(4) *cord blood units on two separate occasions and all labels were adequately affixed to the canisters. The response is acceptable.*

EMERGENCY PRODUCT RECOVERY

LifeSouth has provided a revalidation study for emergency recovery of the units thawed and washed in the transplant centers. In total 3 units were used for this revalidation study. The study included the unit numbers and date of the procedure, and ---(b)(4)----- for post processing ----------(b)(4)----------. In this revalidation study, ----------(b)(4)---------- met the predetermined acceptance criteria.

Reviewer comment*: In the original validation study supporting the emergency recovery procedures, all 3 units tested were shown to be contaminated. Since the rate of contamination during simulated emergency recovery conditions appears to be too high, LifeSouth was asked to provide a revalidation study to support the emergency recovery procedure. In an amendment dated 12/06/2012, LifeSouth provided a copy of completed revalidation study in attachment C of the document. The applicant demonstrated that three out of three units tested for emergency recovery could be recovered without any contamination. The revalidation of the Emergency Recovery is adequate.*

SHIPPING VALIDATION

Validation of Transport for Collected Cord Blood from Hospital to LifeSouth

LifeSouth provided the validation document entitled "Unprocessed Umbilical Cord Blood Transport Containers". The purpose of the validation study was to provide documented evidence that the transport containers can reliably and consistently maintain a temperature between -(b)(4)- when packed with maximum of (b)(4) refrigerated unprocessed cord blood units for transport from various locations to LifeSouth headquarters for processing. The document also provided a list of all collection facilities and approximate distance of each collection site to the centralized cord blood processing center. The minimum distance is 5 miles and the maximum distance is 407 miles. The shipments of unprocessed cord blood were performed using two types of containers, small and large, from hospitals to the processing centers or remote cord blood collection sites. All units used for the validation studies were freshly collected unbankable units and from parents who have signed the permissions to collect form. All cord blood units were stored at refrigerated temperature -(b)(4)- prior to being packed in the container. The temperature of containers during shipment was monitored using data loggers.

The results summarized in the validation document indicated that all small containers failed the acceptance criteria for the shipment, which is the maintenance of unprocessed cord blood unit temp within --(b)(4)-- when challenged with worst case scenarios. In contrast, the larger containers performed better, but with some boxes failing to maintain the desired temperature under certain worst case scenarios. Based on the results submitted, it was not clear if the shipment of unprocessed cord blood was fully validated under all worst scenarios. The applicant was asked in writing to revalidate the transport of shipping containers from the collection site to the processing center.

Reviewers comment: *LifeSouth submitted a revalidation study of storage and transport boxes from collection sites to the cell processing center. According to the results, the larger transport*

boxes were qualified to hold the predetermined temperature range of -(b)(4)--. The validation of shipment from collection sites was performed by 100% monitoring of actual transport temperature using data loggers. The results confirm that the temperature of -(b)(4)-- can be maintained consistently and reproducibly. LifeSouth also commits to --(b)(4)-- requalification of transport boxes during shipment from collection sites to the processing site using min-max data loggers to ensure that the temperature is maintained in the predetermined specified range. The response is adequate.

Validation of Transport from LifeSouth to Transplant Centers:

The ----------(b)(4)---------- dry shipping containers are used to transport frozen CBUs from LifeSouth headquarters to transplant centers. ----------
---

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

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

Reviewer comment: *LifeSouth demonstrated that dry shippers can hold temperature for maximum of (b)(4) under worst case scenario and -(b)(4)-- under ideal conditions. However, it was noted that the acceptance criteria for validation of dry shipper stated that the vapor shippers ----------(b)(4)---------- Since the arrival time is different for different shipments, the applicant should define the acceptance criteria based on the number of days. The validation of the dry shippers as such was deficient and this was identified as an issue to be reviewed as part of the facility inspection. During inspection it was noted that the acceptance criteria for shipping validation was not specified adequately. LifeSouth has revised the acceptance criteria for shipping of the final product. According to the new acceptance criteria shippers ----------(b)(4)----------. The response is acceptable.*

MANUFACTURING FACILITY

The CBU receipt and processing area, QC Laboratory, and all staff and management offices are located at the Corporate Headquarters of LifeSouth Community Blood Centers in Gainesville, Florida. This facility consists of approximately –(b)(4)- square feet. The CBU receipt and processing area, QC Testing Laboratory, and all staff and management offices are located on the first floor of the Operations building on the LifeSouth campus. Cord blood receipt, manufacturing, and storage take place in a dedicated space, consisting of approximately ---------(b)(4)------, including an (b)(4) certified clean room. During inspection the (b)(4) clean room was observed. DMPQ noted several deficiencies in regard to the quality of materials used and unsealed window located in the (b)(4) room and general cleaning procedures (see also the EIR report).

Quarantine and Release Procedures:

LifeSouth employs a combination of paper and electronic methods to track quarantine and release each unit. A more detailed description of the procedure was reviewed in SOP CB.10.6 entitled Review CBU File and CB.10.7 entitled Complete CBU listing in ---(b)(4)------. According to LifeSouth the status of each unit is maintained in LifeSouth Collection Log which includes up to date status of each unit. The Collection Log sheet include the date each unit is received, CBU number, maternal DIN #, weight (grams) of each unit, tare weight, collection date, whether it is discarded during assessment, unit processed or not; unit status (quarantine or released); release date; date removed from ---(b)(4)--- and unit retained for transplant. In addition, LifeSouth has a well defined procedure to update the status of a CBU once its file has been reviewed and approved by the QA Manager. According to this procedure, the status of each unit is updated by initiating entry of each unit status using the ---(b)(4)-----. Detailed information about quarantine and release procedures could also be found in the LifeSouth revised collection log and NMDP CBU report which includes the unit DIN#; local CBU ID, local maternal ID and NMDP ID as well as local registry status.

Contamination/Cross-Contamination:

Cord blood processing is performed in a certified ----------(b)(4)---------- Clean Room. The clean room maintains particulate-free air through the use of HEPA filters. (b)(4) certification requires ----------(b)(4)----------. Validation was completed in September 2011. Contamination and cross-contamination issues are minimized through the use of functionally closed system --(b)(4)-- and single use disposables. The effectiveness of the cleaning process is evaluated by periodic environmental monitoring. During inspection several deficiencies of the clean room were noted as 483 observations (see the EIR for further information). LifeSouth as part of their response to the 483 observation has made several corrective changes to the clean room. The response is acceptable.

Control of Aseptic Manipulations

LifeSouth noted that the aseptic processing has been verified using the *Sterility Protocol Validation*. Additionally, staff are monitoring for aseptic technique at the time of initial training and then periodically thereafter. However, during inspection it was noted that the staff were

not properly trained for aseptic techniques. Operators for example were shown to enter into -(b)(4)-- environments without prior sanitization of their gloves. In addition, operators' skin was exposed during aseptic processing (see also the EIR comments and observation 5 of the 483 form).

Reviewer comment: *LifeSouth, as part of their response to the 483 observations, committed to implement a regular aseptic techniques training for the cord blood processing staff. The response is acceptable.*

Transfers and Additions

During processing, all transfers and additions are performed in a closed environment within a clean room. The processing kit and sample pillows (which are presterilized by the manufacturer) are attached via a sterile docking device, and Hetastarch is added via a sterile syringe through a filter under a biological safety cabinet.

During cryopreservation, DMSO solution (---(b)(4)----) is added through a filtered, single use, pre-loaded, sterile syringe, retaining the closed environment. The product must begin the controlled-rate freezing process -----(b)(4)--------- of DMSO addition. Transfer and addition of reagents to the processing kit and final product appear to be performed under aseptic techniques.

Precautions to Control Contamination

Precautions taken during CBU collection include:

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

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

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

Testing: Monitoring for Contamination

Microbiological testing samples are taken from the final processed CBU. ----------
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----------(b)(4)----------

MATERIALS AND REAGENTS QUALIFICATION:

Each incoming batch of DMSO solution (---(b)(4)--) and Hetastarch is reviewed upon receipt according to LifeSouth's standard operating procedures for supply receipt. For qualification of new lots, visual inspection and verification of the COA and package insert are required. Additionally, DMSO and Hetastarch were qualified for use as part of reagent/supply qualification;

DMSO Qualification:

LifeSouth provided the validation document entitled "DMSO for Cord Blood Cryopreservation". LifeSouth has chosen ---(b)(4)-- manufactured by ----------(b)(4)---------- is a CGMP single use cell cryopreservation media containing dextran 40 and DMSO. To verify the quality of --(b)(4)--, LifeSouth tested the ability of this cryoprotectant to preserve stem cells undergoing -----(b)(4)----------. The results show that the ----------(b)(4)---------- when DMSO was not added to the cryoprotectant. In addition, during the facility inspection, DMSO qualification was reviewed and verified (see also the EIR report).

Hetastarch Expiration Date:

LifeSouth provided the validation document protocol and report for the validation for sterility of Hetastarch ---(b)(4)---- NaCl Injection. The package insert of this product states that the sterile solution is intended for a single use only. The goal of this validation was to determine whether the Hetastarch solution might become contaminated upon multiple uses. The acceptance criteria of the validation were to demonstrate ----------
----------(b)(4)----------
----------. The results of this study shows that the sample collected from the same bag for -(b)(4)-- did not show any positive bacterial growth. Accordingly, the applicant has set the expiration date of --(b)(4)- for the Hetastarch solution.

CONTAINER CLOSURE SYSTEM

The table below lists the containers and closure systems used for CBU collection, processing, and storage. I have reviewed the list of Container Closure used by LifeSouth (see Table 8). The containers for cord blood collection and storage of the final product are

both either approved or cleared by FDA. The overwrap bag product number ---(b)(4)------ does not have direct contact with the product. However, it has been qualified as part of -----(b)(4)--------- Validation.

Table 5: Container Closure Information Summary

Container / Closure System	Manufacturer	Testing Results or related FDA #
Cord blood sterile collection bag	---------- ---------(b)(4)---------- ----------	---------- ----(b)(4)----
----------(b)(4)-------- ----------	---------- --------(b)(4)--------- ------- ----------	---------- ----(b)(4)---
Overwrap bags ----(b)(4)-----	---------- ----(b)(4)--- ----------	-------- ----(b)(4)------ ---------- ----------

STERILITY TESTING AND METHOD VALIDATION

The applicant (LifeSouth Community Blood Center) provided information on their sterility test and data for the respective method validation in the following submissions:

1. Original submission (STN 125432\0, Volume C, pages C197 - C236)
2. Amendment 11 (STN 125432\0.11, submitted on 01/30/2013)
3. Amendment 17 (STN 125432\0.17, submitted on 03/15/2013)
4. Amendment 19 (STN 125432\0.19, submitted on 04/19/2013)
5. Amendment 18 (STN 125432\0.18, submitted on 05/16/2013)

Proposed Sterility Test Procedure and Lot-release Specification (From STN 125432\0.17, 0.19 and 0.18):

1. The Applicant has proposed to use ----------(b)(4)---------- with ----------(b)(4)---------- culture media for the sterility test.
2. The proposed test sample is a ---------(b)(4)---------- processed from the same cord blood unit.
3. The proposed incubation time and temperature are ----------(b)(4)----------.
4. The proposed product release specification is no growth in both aerobic and anaerobic culture bottles.

Note: *The above test sample and incubation temperature (from STN 125432\0.17) are different from those proposed in the original submission (STN 125432\0). For more explanation please see the reviewer's comments under "Sterility Test Method Validation".*

Written Description of the Sterility Test:

The Applicant has submitted information on the working principle of the ----------(b)(4)---------- and standard operating procedures (SOP) for sample processing (SOP CB.7.2.4), culture bottle inoculation (SOP (b)(4)), incubation (SOP---(b)(4)----) and result interpretation (SOP ---(b)(4)----).

Reviewer comment:

1. *The information submitted on the composition of the culture media and incubation conditions are adequate and acceptable – complies with 21 CFR § 610.12 (c)(1)(i)(A) and 21 CFR § 610.12 (c)(1)(i)(C).*
2. *During assay validation the applicant found that the ----------(b)(4)----------.*

Culture Media Qualification:

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the fact that the processed HPC, Cord Blood final product is not suitable for terminal sterilization, the LifeSouth HPC, Cord Blood final product should not be labeled as sterile and a warning should be put in the label regarding the potential to transmit infectious bacteria or fungi.

Other Test Methods:

Table 12: Other Test Methods

Test Typ	Test Name	Description, samples used	Laboratory	Reference Standard
Hemoglobin testing	---(b)(4)--- ---------	--------(b)(4)---------- ----------	-----(b)(4)------ --------	Performed in a CLIA- certified and CAP accredited laboratory;
TNC counts	-------- --(b)(4)-- -------	---------- ---------- ----------(b)(4)---------- ---	LifeSouth QC Laboratory, Gainesville,	Performed on site in a CLIA-certified and CAP and AABB
Nucleated cell viability assay(s)	------- ----(b)(4)---- -------- ---------- ------ ------	---------- (b)(4)----------	LifeSouth QC Laboratory, Gainesville, Florida	Performed on site in a CLIA-certified laboratory.
CD34+ cell viability ---(b)(4)---	----(b)(4)--Flow Cytometery -------(b)(4)---- ---------- ---------- ----------	---------- (b)(4)----------	LifeSouth QC Laboratory, Gainesville,	Performed on site in a CLIA-certified laboratory.
HLA typing	---------- ---------(b)(4)---------- ----------	---------- -------(b)(4)----- ----------	--------, ------(b)(4)---- --- ---------- ------	Performed in a CLIA- certified and ASHI accredited laboratory.
ABO blood group and Rh type	--------- --(b)(4)--	---------- -------(b)(4)---- ---------- ----------	LifeSouth QC Laboratory, Gainesville,	Performed on site in a CLIA-certified and CAP and AABB accredited laboratory.
------- --(b)(4)---- ------	---------- ---(b)(4)----	---------- ------(b)(4)--------- --------	---------- ---(b)(4)--- -------- -----	-----(b)(4)-----.

Test Typ	Test Name	Description, samples used	Laboratory	Reference Standard
Nucleated red blood cell counts	---------- ---------- ---------- ---------- -----(b)(4)--- ---------- ----------	---------- ----------(b)(4)------- ----------	LifeSouth QC Laboratory, Gainesville, Florida	Performed on site in a CLIA-certified laboratory.

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

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

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

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

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

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

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

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

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

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

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

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

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[(b)(4)]

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

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

----------(b)(4)----------
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CD34 Enumeration and Viability Assay Validation:

Validation Strategy: The applicant used a well-established --(b)(4)- protocol which has been approved and validated by CLIA. They submitted validation data to show that the --(b)(4)-- assay works well in their facility. Parameters chosen by the applicant for validation included precision, accuracy, and linearity. For this assay, precision of the CD34 cell count is the most important parameter since potency is based on this count.

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

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

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nRBC Method Validation by ----(b)(4)----------:

Assay Overview:

LifeSouth validated a laboratory developed protocol for enumeration of nucleated red blood cells (nRBCs) in cord blood units (CBUs). Automated nRBC determination is a requirement by FACT and NMDP Standards. ----------
----------(b)(4)----------
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----------(b)(4)----------

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nRBC Enumeration Assay Validation:

Validation Strategy: The important parameters for nRBC validation include specificity, accuracy, precision, linearity, and limit of detection. Parameters the applicant addressed included accuracy, precision, linearity, and limit of detection. ----------
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----------(b)(4)----------
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----------(b)(4)----------

[(b)(4)]

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

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

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

Hemoglobin test method:

LifeSouth uses a contract testing lab, ----------(b)(4)---------- Hemoglobinopathy Reference Laboratory, to perform hemoglobinopathy testing. The Hemoglobinopathy Reference Laboratory at (b)(4) serves as the reference laboratory for the ------(b)(4)----------, as well as provides hemoglobinopathy testing for other major cord blood centers across the country.

Reviewer comment*: The applicant provided limited details for the test method in the BLA submission. Additional details regarding the method and validation were provided during the PLI and added to the BLA as an amendment (dated 11/1/2012).*

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

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

Reviewer comment: *LifeSouth sends (b)(4) cord blood samples taken from----------(b)(4)----------. However, the applicant states that the Hemoglobinopathy Reference Laboratory prefers receiving ----------(b)(4)----------, as the test sample and use of this sample type has been appropriately validated per the CLIA requirements for a clinical testing lab (see reviewer comments under method validation). This is acceptable.*

Acceptance Criteria: No homozygous hemoglobinopathy

Method Validation: As hemoglobinopathy testing is performed by a contract testing lab, LifeSouth has not provided their own method validation information. However, the contract testing laboratory, the ----------(b)(4)----------, is CLIA-certified (CLIA ID #: ---(b)(4)-----) and CAP accredited to perform hemoglobin testing and the relevant certificates have been provided. As the ----------(b)(4)---------- is CLIA certified and CAP accredited to perform hemoglobinopathy testing, FDA does not require additional test method validation.

Reviewer comment*: CLIA regulations (42 CFR 493.1253) outline the requirements for establishment and verification of performance specifications, e.g. validation, for all tests used in CLIA certified testing labs. LifeSouth has provided the CLIA certifications and CAP accreditation information for (b)(4). The method is suitable for its intended purpose.*

Total Nucleated Cell Count (TNCC):

Method Description: LifeSouth's QC laboratory measures the Total Nucleated Cell Count (TNCC) of CBUs ----------(b)(4)----------

[(b)(4)]

***Reviewer comment**: Minimum pre-processing TNCC was not defined in the BLA submission. Upon request, the reference document "CBU weight and TNC level requirements" (revision Jul2012) was provided in an amendment to the BLA (submitted 8/24/12). This document specifies a minimum gross CBU weight of ------(b)(4)----- sterile collection set (including needle guard and labels) and minimum pre-processing TNC level which is categorized by race according to the table above. The sponsor also explained that the different minimum gross CBU weight(b)(4) used for the collection validation study was based on the bag tare weight that was obtained at the time. This is acceptable.*

It was observed on the PLI that it is possible on any given day for more incoming CB units to meet processing eligibility than can be processed at current capacity --(b)(4)--. The applicant had no written SOPs to address this situation. The lack of written procedures to describe criteria for selection of units for further processing after initial accessioning was issued as a 483 citation (see EIR for details). The applicant has since updated the SOP CB.7.1.2 as part of their 483 response (submitted in amendment dated 11/13/12) to clearly outline criteria for selection of units for further processing if the capacity is exceeded. These criteria are based on ----------
----------(b)(4)----------
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----------(b)(4)----------

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

Human Leukocyte Antigen (HLA) Typing (initial and confirmatory typing):

Human Leukocyte Antigen (HLA) typing is performed by contract through the ------(b)(4)----------. The -(b)(4)- utilizes two CLIA certified and ASHI accredited laboratories for HLA typing: ----------(b)(4)---------- and -------(b)(4)----------. Initial HLA typing is performed on a sample of red blood cells from the cord blood unit (CBU) after processing. The results from this initial typing are reported. They are critical to ensuring the identity of the final product and to enhancing the likelihood of a successful transplant through computerized matching with the potential recipient. ----------(b)(4)----------

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----------(b)(4)----------
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The applicant has provided their vendor qualification criteria for contract laboratories per SOP QA.4.1.

***Reviewer comment**: The method description and validation are satisfactory given that CLIA certified and ASHI accredited laboratories organized through (b)(4) perform the testing. As described above, CLIA regulations (42 CFR 493.1253) outline the requirements for establishment and verification of performance specifications, e.g. validation, for all tests used in CLIA certified testing labs. LifeSouth has provided the CLIA certifications and ASHI accreditation information for the (b)(4) contract laboratories. The method is suitable for its intended purpose.*

ABO blood group and Rh type test method:

Method Description: The ABO blood group and Rh (D) type is determined by the ---(b)(4)---------- using FDA licensed reagents per SOP IMMU.3 by trained personnel in the LifeSouth QC Laboratory. ----------
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----------(b)(4)----------

***Reviewers comment**: SOP IMMU.3 has been provided upon request (amendment dated 9/7/12).*

Acceptance Criteria: All blood groups and Rh types are acceptable. Pre- and post-processing ABO types must match.

Method Validation: The LifeSouth QC laboratory is CLIA certified (CLIA #10D0987839) and CAP and AABB accredited to perform ABO/Rh typing. The accreditation process includes an onsite inspection of the facility (2 year cycle) and, for CAP, an interim self-inspection. Inspection checklists guide the CAP-accreditation and self-inspection process. The following CAP checklists apply to ABO/Rh typing methods:

- Laboratory General Checklist: reviews general laboratory items including test method verification/validation.

- Transfusion Medicine: reviews records related to the ABO/Rh and Weak D testing methods.

Additionally, LifeSouth participates in a proficiency testing through CAP ------(b)(4)---------. The relevant survey description which includes ABO and Rh type is immunohematology (CAP code J).

Reviewer comment: *The method description and validation are satisfactory given that the LifeSouth QC laboratory is CLIA certified and CAP and AABB accredited to perform ABO/Rh testing. As described above, CLIA regulations (42 CFR 493.1253) outline the requirements for establishment and verification of performance specifications, e.g. validation, for all tests used in CLIA certified testing labs. LifeSouth has provided the CLIA certifications and CAP and AABB accreditation information. The method is suitable for its intended purpose.*

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

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

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

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

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

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

LABELING

Cord Blood Donor Tracking:

At the collection hospital, units are labeled with the maternal identification label generated by the hospital (includes birth mother's name, medical record # and date of birth) and the unique donor identification number (DIN) sticker. LifeSouth uses the ISBT 128 data structure for the DIN. The ISBT 128 number includes the facility identification number (FIN), year and 6-digit serialized unique identifier.

Example of DIN: FIN (W2434) + Year (12) + serialized ID# (111111)

Reviewer comment: *In the initial BLA, LifeSouth did not provide adequate information regarding the DIN assigned to the cord blood unit and the maternal specimens and the process for maintaining linkage. In the amendment submitted on 11/13/2012, LifeSouth provided the following clarification:*

> *DINs with FIN "W2434" are assigned to the cord blood unit*
> *DINs with FIN "W1151" are assigned to the maternal specimens*

LifeSouth also explained that in addition to the maternal identification label that is generated by the hospital and placed on the collected unit, the DIN assigned to the cord blood unit is placed on the collection bag and on the CBU Collection Form at the hospital. To maintain linkage, the DIN assigned to the maternal specimens is placed on the same CBU Collection Form at the LifeSouth Headquarters. As an additional measure for linkage, the cord blood unit and the maternal specimen DINs are entered into the (b)(4) computer system. The cord blood unit and the maternal DINs are also listed on the donor medical history questionnaires, the summary of the infectious disease test results and the Final Declaration of Eligibility form that are sent to the transplant centers. LifeSouth submitted SOPs CB4.1, CB6.1, CB.5.3; and the flowchart entitled Overview of DIN Assignment and Linkage in the amendment dated 12/19/2012. The process for donor tracking is acceptable.

Barcode Label:

For labeling LifeSouth requested an exemption from the bar code label requirements (21 CFR 201.25(d)). LifeSouth stated that they intend to use ISBT symbology. LifeSouth also provided draft labels for 1) Container label; 2) Package label/Shipper label (see below):

Figure 3: Original container label

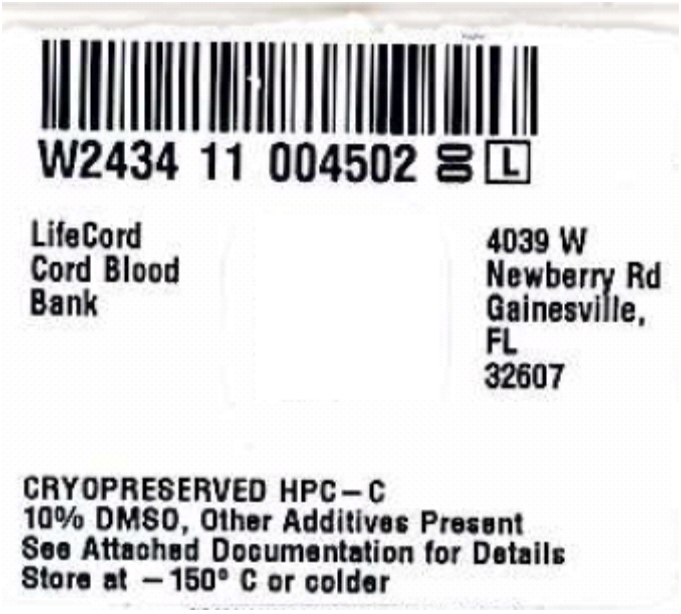


Figure 4: Original package label

Hematopoietic Progenitor Cells, Cord Blood

LOCAL UNIT ID# **Label prepared by:**

NMPD UNIT ID# **Verified by:**

Total Cryopreserved Volume: 25 mL
10% DMSO; other Additives Present. See Attached Documentation for Details. Refer to the enclosed Package Insert for complete product details.

Total Nucleated Cells: **Total CD34 Cells:**

Recommended Temperature of Storage ≤ -150° C	R X O N L Y
COLLECTED AND PROCESSED BY: LifeSouth Community Blood Centers 4039 Newberry Road Gainesville, FL 32607 U.S. License Number 1647	DO NOT IRRADIATE DO NOT USE LEUKOREDUCTION FILTERS EXPIRATION DATE:_____ *(expiration assigned at time of shipment based on stability studies)* *FORM CB.11.8, May2012*

Reviewer comment*: The draft label contains Donor Identification Number (DIN) but does not include the product code. In a telecon dated October 24, 2012 we discussed the need for including the product code. LifeSouth agreed to include this information on the container label.*

In telecon dated August 28, 2012 we requested that LifeSouth to comply with the ISBT in regard to the draft package label. LifeSouth in amendments dated 11/1/2012 and 11/13/2012 agreed to fully implement the ISBT-128. A revised version of container label including the product and facility codes and a copy of the revised package label were submitted (see below). The new container and package labels appear to be compliant to the ISBT-128. The response is adequate.

Figure 5: Revised container label

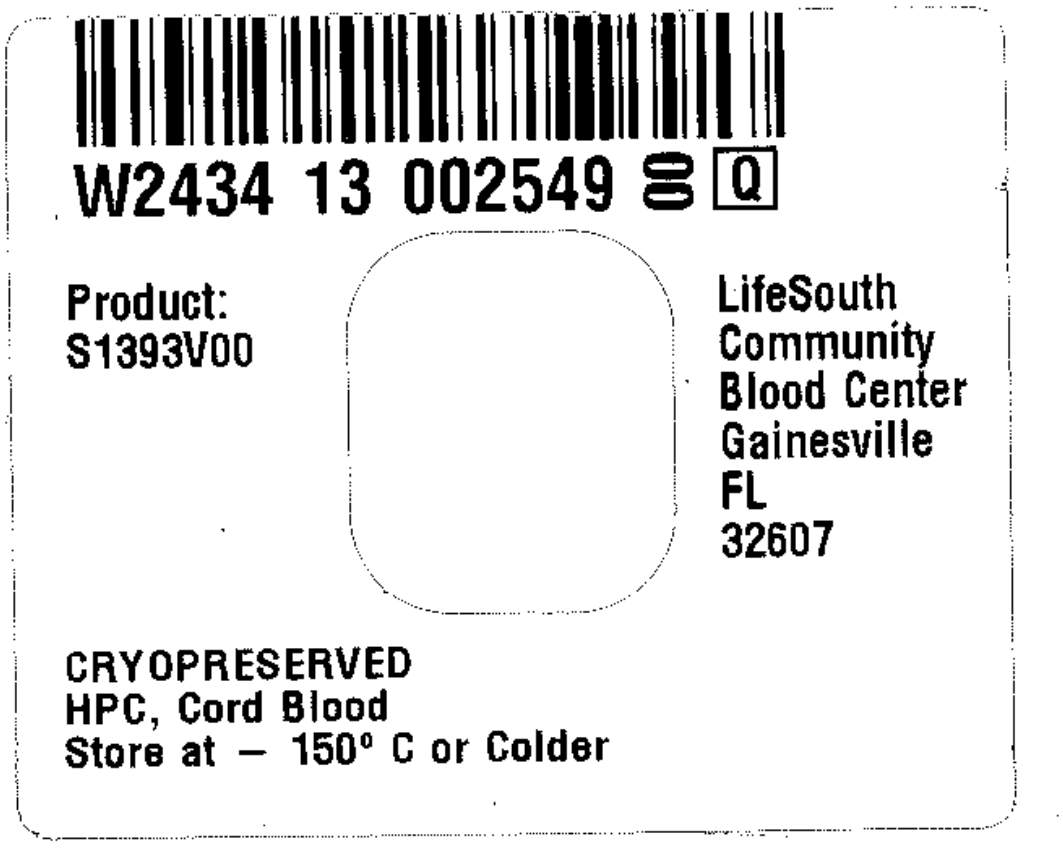
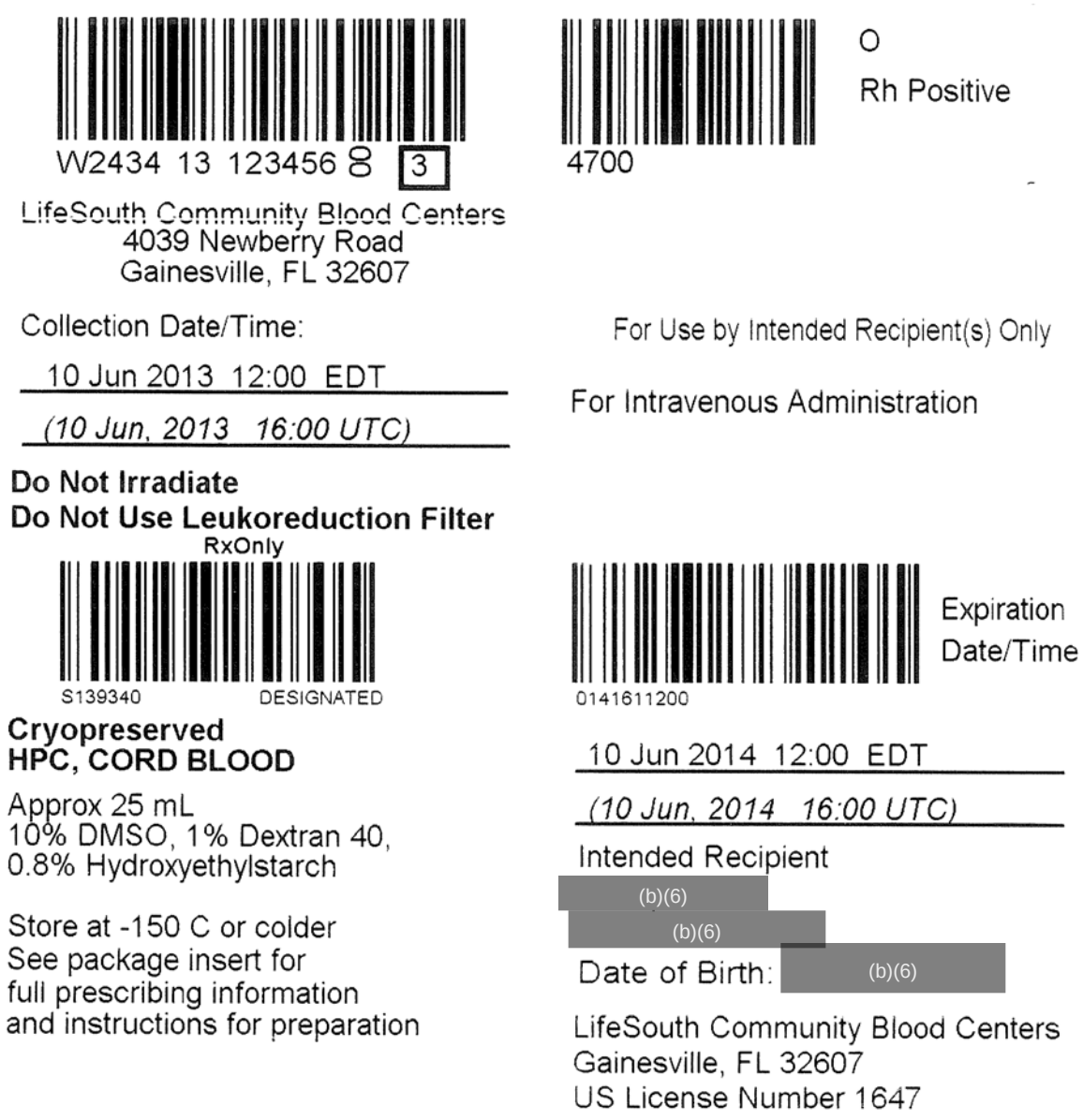


Figure 6: Revised package label



PROPRIETARY NAME

The applicant proposed ----(b)(4)--- as the proprietary name for their product on February 1, 2013. The proposed proprietary name was reviewed in consultation with CBER's Advertising and Promotional Labeling Branch (APLB) and it was found unacceptable. The basis for the decision was that the name is the ----------(b)(4)----------, with the meaning of lifesaving cells or cells providing life, misleadingly implies

that the product has survival effectiveness beyond that supported by the data. The decision was communicated to the applicant on March 22, 2013 via regular mail and in a teleconference on March 27, 2013. In a letter sent on March 27, 2013, LifeSouth indicated that they decided not to request an alternate proprietary name and they intend to use the proper name, HPC (hematopoietic progenitor cells), Cord Blood, for their product.

STABILITY PROGRAM

LifeSouth has provided a protocol for stability studies aimed to: 1) Establish storage duration of thawed, cryopreserved HPC, Cord Blood based on prospective analysis of stability data from inventory collected since LifeSouth set up a new processing center for HPC, Cord Blood in October 2011; 2) Submit prospective testing data from HPC, Cord Blood processed and frozen using methods following the *Guidance for Industry: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products* for HPC, Cord Blood, and 3) Permit requests for future extension of the expiration dates as data are acquired.

As part of the stability study LifeSouth committed to provide sterility, identity, purity and potency of the units post thaw (see table below).

Table 18: Acceptance Criteria for Stability Study Protocol

Attribute	Test	Testing method	Result acceptance criteria: FDA-guidance
Sterility	Bacterial/fungal contamination	Bacterial/fungal cultures required in 21CFR 211.165(b) and 21 CFR 610.12 using a validated, automated microbial assay system.	• No growth at 35°C of either anaerobic or aerobic micro-organisms at 14 days incubation • No fungal growth at 25 °C after 14 days of incubation
Identity	Verification of DIN	Two person double verification technique of associated DIN for CBU	DIN being removed from ---(b)(4)---- equipment matches the DIN being requested for thawing
Purity	Total Nucleated Cells (TNC) Total CD34+ Cells	Cell counting instrumentation CD34+ (b)(4) enumeration by flow cytometry	------(b)(4)---------
Potency	Viable Nucleated Cells	-----(b)(4)---------- ---------- non-viable and viable cells	----(b)(4)-------
Quality	% Recovery, after manufacturing and storage Transplantation outcomes	Calculation based on cell counting methods used Outcomes data provided by transplant centers	TNC recovery (b)(4) CD34 % recovery ---(b)(4)----- Transplant outcomes equal to –(b)(4)- data; if information does not match, investigation required.

LifeSouth has proceeded with a stability protocol by initially using a minimum of (b)(4) CBUs or (b)(4) of the projected annual banking rate of (b)(4) HPC, Cord Blood that are representative of the manufacture, storage, and scale of production. For units manufactured during 2012, three will be thawed and tested for stability after pre-determined months of storage. At the end of this time, if all data are acceptable, three units will be tested ---(b)(4)--- for up to (b)(4). For units manufactured during 2013, three units will be thawed and tested for stability after ----(b)(4)------ of storage, then ---(b)(4)--- for up to ---(b)(4)----. For units manufactured during 2014 and subsequently, 3 units will be thawed and tested for stability ---(b)(4)--- for a minimum of (b)(4).

At the time of submission, LifeSouth proposed 1) a 2-hour expiration of the thawed and washed CBU, 2) periodic submission of additional stability data after processing to determine the maximum storage date for the time period supported by new data, and 3) submission of post-transplant patient outcome data provided by transplant centers and/or donor/transplant registries. The data submitted in support of 2 hour expiration for unit thawed, washed and stored at room temperature or 4 °C in the transplant centers are adequate. However, LifeSouth did not provide sufficient data supporting the initial expiration date of proposed units to be licensed. In a telecom dated July 31, 2012 we asked for data supporting the expiration date for the proposed licensed units. The LifeSouth response detailed below is acceptable.

LifeSouth Response:

The LifeSouth Stability Protocol has been updated based on the information provided in Guidance for Industry Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications (October 2009). LifeSouth has also revised the stability study protocol entitled "Stability Study Protocol for Hematopoietic Progenitor Cell, Cord Blood (HPC, Cord Blood) submitted to the FDA in the addendum documents from addendum sent November 14, 2012. The changes in the Stability Study Protocol will reflect the purity measure of (b)(4) recovery for total nucleated cells (TNC) and the potency measure of (b)(4) recovery of viable CD34+ percentage. The changes in the Stability Study Protocol also reflect the addition of testing at time intervals post-thawing and washing of the CBU immediately after thawing and washing and 30 minutes post-thawing and washing to more closely represent the conditions present during transplant. LifeSouth has performed stability studies on (b)(4) cord blood units to date. The expiration date of HPC, Cord Blood based upon the stability study data is currently 11 months. Stability studies were performed on cord blood units at 4, 5 and 11 months. LifeSouth has made a commitment to perform additional stability studies on cord blood units at the one year mark and ongoing as outlined in LifeSouth's Stability Study Protocol for Hematopoietic Progenitor Cell, Cord Blood (HPC, Cord Blood). The response is acceptable.

COMPUTER SYSTEMS

A list of computer systems used at LifeSouth is summarized in table below. Systems include ----------(b)(4)---------- used for recording the maternal eligibility ad maternal testing results, ---(b)(4)------- used for tracking and distribution of HPC, Cord Blood and associated samples; ----------(b)(4)---------- used for controlled rate freezing and storage; automated readers (--------(b)(4)---------- designed to capture lot information for processed cord blood. Computer systems were evaluated by DMPQ during the inspection. However, it is noted that the system for recoding the results of donor eligibility is cleared for blood banks only. During inspection we were able to verify that (b)(4) system used for recording the donor eligibility has been modified using proper change control procedures.

Figure 7: Computer systems overview

System Type	Name of System	Manufacturing Steps it Controls	Developed by
Recording results of donor eligibility screening and testing	---------- -----(b)(4)--------- ----------	Maternal eligibility Maternal testing results	in-house (LifeSouth); 510(k) approval by FDA[2]
Tracking distribution of HPC, Cord Blood and associated samples	----(b)(4)-----	Location of CBU CBU Listing Confirmatory Typing (CT) request for CBU Distribution of CBU and samples	contractor/vendor (b)(4)

System Type	Name of System	Manufacturing Steps it Controls	Developed by
Controlled rate freezing and storage	---------- ---------- ------(b)(4)--------- ----------	Cryopreservation (controlled rate freezing) Storage and retrieval	----(b)(4)------
Automated reader	---(b)(4)---	---------- ----------(b)(4)---------- ---------- ----------	---(b)(4)---
Captures lot information for CBU processing	---(b)(4)---	Data capture during Processing of CBU on (b)(4)	---(b)(4)--
--(b)(4)---	--(b)(4)--	-----(b)(4)----------	---(b)(4)-----

RESERVE SAMPLES

Reviewer comment: *LifeSouth did not provide a detailed description of their retention sample program in the original submission, but provided information in response to several FDA information requests, as outlined below. LifeSouth's responses are adequate.*

1. *Please provide a more detailed description of the reserve sample(s) that you maintain for each lot of your product (see 21 CFR 211.170). Please include a description of how the sample(s) is obtained and stored along with an explanation of the testing that could be performed on the sample(s).*

2. *Regarding SOP CB.11.6.2 (Volume B, page B-287) you state that the HPC, Cord Blood segment viability must be ------(b)(4)----------. Please clarify if you intend to transplant units which have post thaw viability of less than 85%..*

LifeSouth Response:

LifeSouth provided a summary of SOPs CB.7.2.4, CB.8.3.1, QCL-CB.1.2, QCL-CB.1.4 and CB.8.3.3. ----------
----
----------(b)(4)----------

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

ENVIRONMENTAL ASSESSMENT

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