MEMORANDUM

CMC Review of Original Submission

BLA 125413

HPC, Cord Blood

St. Louis Cord Blood Bank (SLCBB)

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

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EXECUTIVE SUMMARY

Recommendation: There are deficiencies in the Biologics License Application (BLA) that must be addressed before a license can be granted. We recommend that a Complete Response letter be issued to communicate the deficiencies and information that is required to complete our review.

Product overview: The St. Louis Cord Blood Bank (SLCBB) seeks to license cryopreserved Hematopoietic Progenitor Cells (HPCs) that have been derived from cord blood. The BLA is for HPC, Cord Blood intended 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**.**

SLCBB proposes to license cord blood processed using the PrepaCyte-CB method that enriches the product for white blood cells while depleting red blood cells (RBCs) and plasma. The PrepaCyte-CB kit has been cleared via a 510(k) (BK070067) and is also described in MF (b)(4). The final HPC, Cord Blood product consists of approximately 25 mls of processed cord blood cryopreserved in 10% Dimethyl sulfoxide, and 1% Dextran 40.

The HPC, Cord Blood product is manufactured at two sites. The primary site, where the majority of the cord blood units are processed, is located adjacent to the Cardinal Glennon Children's Medical Center (CGCMC) and the St. Louis University (SLU) Medical School campus. The second manufacturing site is at the St. Luke's Cancer Institute in Kansas City, MO (SLCI).

Material reviewed: The original submission and amendments through SN11 received on 6/26/12, were considered in this review. SN12, which was received on 8/1/12, was not reviewed in this cycle.

Overview of Review Findings: The major CMC review issues that have not been resolved during the review process are listed below. Items 1 – 5 are common to both manufacturing sites. Additional deficiencies identified during the review process are present in the Complete Response letter comments.

1. Validation of the cord blood collection and processing procedures has not been completed.

2. SLCBB has verbally indicated that they plan to implement ISBT (International Society of Blood Transfusion) 128 for labeling and tracking. However, no documentation related to the use of this standard has been submitted for review.

3. SLCBB has not identified a suitable retention sample.

4. Updated sterility testing SOPs need to be submitted for review to ensure that all review issues have been addressed.

5. Updated SOPs pertaining to cord blood collection and donor eligibility still need to be submitted for review.

6. Inadequate validation data was submitted for SLCI's sterility testing, viability testing, CD34 cell enumeration, and total nucleated cell counting.

Inspection Findings: The inspection of the St. Louis (SLCBB) manufacturing site occurred April 16 – 20, 2012, and the inspection of the Kansas City (SLCI) manufacturing site occurred April 23 – 27, 2012. The 483 for the St. Louis manufacturing site contained 9 observations and the 483 for the Kansas City manufacturing site contained 12 observations. Major unresolved observations for the St. Louis and Kansas City manufacturing sites include the following:

1. Process validation for the manufacture of the Hematopoietic Progenitor Cell, Cord Blood has not been completed.

2. Documented evidence is lacking to demonstrate the Quality Control Unit (QCU) performs all of their defined roles and responsibilities included in SOP QM.02.03. For example,
    a. the QCU does not approve Standard Operating Procedures or protocols prior to use, and
    b. the QCU is not the entity who determines release of raw materials.

3. There is inadequate segregation to prevent mix-up and cross contamination. For example, during observation of the manufacturing process ----------(b)(4)----------.

Complete Response Letter Comments:

Process Validation

1) The collection validation summary that you have submitted is not adequate because it does not include all the relevant aspects of the collection procedures that are currently in use (e.g. completion of donor screening documentation, labeling, collection volume, and transportation) with pre-defined acceptance criteria. Please submit the final validation summary for the collection and transportation of cord blood units from the hospitals to the processing laboratories. The validation must be completed at SLCBB and SLCI facilities.

2) Please submit PrepaCyte-CB processing validation protocols. You will need to establish a validation protocol, with defined acceptance criteria, that is approved by your Quality Unit before performing the validation study. The protocol should be developed using any new SOPs that are implemented in response to the 483 inspection observations.

3) The thawing and reconstitution instructions to be provided in the Prescribing Information must be based on validated procedures. Please provide written instructions and data demonstrating that your instructions have been validated.

Retention Sample

4) Please identify an appropriate reserve sample that will be retained for each lot in compliance with 21 CFR 211.170. One of the segments attached to the cryopreserved HPC, Cord Blood product may be appropriate.

Stability

5) The data that you have submitted are insufficient to establish a product dating period (expiration date). We note that only summary data were included, and no stability protocol has been established. Please provide a stability protocol and data to establish an expiration date for cryopreserved HPC, Cord Blood units made using the PrepaCyte-CB process. The stability protocol should contain appropriate predefined acceptance criteria.

Sterility

6) The submitted validation data do not adequately support a (b)(4) incubation time for the sterility test. For testing the sterility of the licensed product please incubate all samples for 14 days.

7) Please update your standard operating procedure (MI.02.01) showing the validated incubation time, and temperature, the --(b)(4)-- culture -(b)(4)- used, and how qualification of each lot of --(b)(4)-- culture -(b)(4)- will be performed. Please submit the updated SOP for FDA review.

8) No validation data for sterility testing at SLCI were submitted. Please submit these data.

Collection

9) For collected units transported from the hospitals to the SLCBB facility, the transportation SOP should clearly define whether or not you discard units if there is any temperature excursion during transportation of units. Furthermore, we do not feel that your existing measures are adequate to ensure that the appropriate temperature is maintained throughout the shipping procedure. We recommend that a continuous temperature monitor be utilized for each shipment to ensure that the temperature is maintained throughout shipping and storage and that the data be reviewed before units undergo further processing.

10) The SLCI facility SOP SLCI-CTS 4039.01 states that the acceptable transportation temperature is (b)(4). However, it is not clear if a continuous temperature recording device (e.g. data logger) or a thermometer that simply displays the temperature is used in the transport coolers and whether units are discarded if the transportation temperature is outside the defined range. Please provide clarification and describe how you will ensure that the appropriate temperature is maintained during the entire transit time.

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

Donor Eligibility

12) Please submit the final Donor Eligibility (DE) SOPs/forms used at the SLCBB and SLCI facilities. The final SOPs/forms should address the following issues in the draft SOPs submitted on 6/26/12 (SN10):

    a. Draft SOP CL.03.07: Please clarify whether donors with the listed findings are considered "eligible" or "ineligible" for DE determination purposes and specify that donor conditions such as elevated temperature in mother/infant or receipt of antibiotics during labor are acceptable only in absence of any suspicion related to infection.
    b. Draft SOP CL.06.08: Please define how information regarding the possibility of plasma dilution in the birth mother (e.g. administration of >2000ml IV fluid) is factored in to the DE determination.
    c. Draft Product Documentation/Tech Review form: There is no category for HPC, Cord Blood units collected from donors for whom DE was not

completed and it is not clear whether an HPC, Cord Blood unit categorized as "available", is acceptable for licensure or release under IND.
Also, please submit the corresponding form used at SLCI.

13) In SN10, received on 6/26/12, you stated that the CMV (b)(4) is performed on the (b)(4) sample of the unit. We note that you will not release the product if the CMV (b)(4) result is positive. Therefore, we consider this to be a release criterion and the assay must be validated.

14) Please provide information regarding the unique donor identification numbering system that is used at the SLCI facility.

15) Please submit the maternal specimen shipping information for the SLCI facility.

Assay Validation

16) We note that no data were provided for the ----------(b)(4)---------- at SLCI. Please submit qualification data on this instrument, including analysis of cord blood samples for relevant parameters (e.g., WBC, nRBC).

17) Regarding your SN03 submission (Req 4b: 2/4, submitted 12/13/11) that included cell count "linearity data" for the SLCI ----------(b)(4)----------, please clarify the types of samples tested and clarify your acceptance criteria.

18) Adequate information was not submitted to evaluate SLCI's use of ----(b)(4)---- as a primary method for viability testing. Please submit SLCI's method comparison of cord blood viability using ----------(b)(4)---------- and an evaluation of viability sample stability.

19) Inadequate information was submitted to evaluate SLCI's use of ------(b)(4)------ to enumerate viable CD34+ cells in cord blood samples. Please address the following concerns:

a) Please submit qualification data for the ----------(b)(4)---------- that includes analysis of cord blood samples for relevant parameters (e.g. CD34/-------(b)(4)-------).
b) Regarding the SLCI report titled "New Instrument Validation ----------(b)(4)---------- (re: SN03 submission, Req 4b, 3/4) please provide additional description on the type of samples analyzed throughout this report and clarify the acceptance criteria for all parameters.

20) Inadequate information was submitted to evaluate inter-laboratory precision of cord blood ------(b)(4)------ comparison between SLCI and SLCBB (re: SN03 submission, Req 4b, 4/4). Please clarify your acceptance criteria used for this comparison.

Labeling

21) In the 7/30/2012 telecon, you stated your intention to implement a container and package label system according to ISBT128. Please submit revised container and package labels.

22) We note you have included the name "AlloCORD" on your example of a proposed label to be affixed to the HPC, Cord Blood product. Please submit a proprietary name request according to Guidance for Industry "Contents of a Complete Submission for the Evaluation of Proprietary Names" available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf

GENERAL INFORMATION

The St. Louis Cord Blood Bank (SLCBB) seeks to license cryopreserved hematopoietic progenitor cells that have been derived from cord blood. The Biologics License Application is for use of HPC, Cord Blood 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. SLCBB only wants to license HPC, Cord Blood processed using the PrepaCyte-CB method, which they have been using since November, 2009.

The SLCBB is owned by SSM (Sister of St. Mary) Cardinal Glennon Children's Medical Center (CGCMC), reporting to and operating under SSM's Corporate Structure. Primary manufacturing facilities and staff offices are located in approximately 10,000 square feet of space in the Pediatric Research Institute (PRI) building adjacent to CGCMC and the St. Louis University (SLU) Medical School campus, Hospital and Cancer Center. Designed as a community-based program, the SLCBB utilizes an obstetrician collection model with participation of over 400 physicians and midwives. The SLCBB retains active agreements with 29 hospitals in the metropolitan St. Louis region (eastern Missouri and southern Illinois) and four hospitals in the Kansas City region.

The SLCBB primary manufacturing site is accredited by the AABB (formerly the American Association of Blood Banks) and the College of American Pathologists (CAP), regulated by the Centers for Medicare & Medicaid Services (CMS) through certification specified in the Clinical Laboratory Improvement Amendments (CLIA), and registered with the Food and Drug Administration.

In July 2008, the SLCBB entered into a contract manufacturing arrangement with St. Luke's Cancer Institute in Kansas City MO (SLCI) to collect and process cord blood products in their facility. The SLCI facility processes cord blood under the direction of the SLCBB using the same SOPs for cord blood processing and product testing. The SLCBB reviews all batch records for product safety, purity, and potency prior to approval for transport to the SLCBB site. The Kansas City site is accredited by the Foundation for the Accreditation of Cellular Therapy (FACT), CAP, and CLIA. Products manufactured at the SLCI site will bear the label proposed in this application, and the processing site will be identified in the accompanying records.

Cord Blood Processing Sites

St. Louis Cord Blood Bank	3662 Park Avenue, St. Louis, MO 63110
St. Luke's Cancer Institute	4401 Wornall Road, Kansas City, MO 64111

Collection Sites

Anderson Hospital -	Maryville, IL 62062
Alton Memorial Hospital -	Alton, IL 62002
Barnes-Jewish Hospital -	St. Louis, MO 63110
Barnes-Jewish St. Peters Hospital -	St. Peters, MO 63376
Blessing Hospital -	Quincy, IL 62305
Memorial Hospital of Carbondale -	Carbondale, IL 62902
DePaul Health Center	Bridgeton, MO 63044
Jefferson Regional Medical Center	Crystal City, MO 63019
Gateway Regional Medical Center	Granite City, IL 62040
Belleville Memorial Hospital	Belleville, IL 62226
Mineral Area Regional Medical Center	Farmington, MO 63640
Missouri Baptist Medical Center	St. Louis, MO 63131
Parkland Health Center	Farmington, MO 63640
Perry County Memorial Hospital	Perryville, MO 63775
Progress West Health Center	O'Fallon, MO 63368
St. Anthony's Health Center	Alton, IL 62002
St. Anthony's Medical Center	St. Louis, MO 63128
St. Clare Health Center	Fenton, MO 63026
St. Elizabeth's Hospital – Belleville	Belleville, IL 62220
St. Francis Medical Center	Cape Girardeau, MO 63703
St. John's Mercy Medical Center	St. Louis, MO 63141
St. John's Mercy Hospital	Washington, MO 63090
St. Joseph's Hospital-Breese	Breese, IL 62230
St. Joseph's Hospital West	St. Louis, MO 63367
St. Joseph's Health Center	St. Charles, MO 63301
St. Luke's Hospital	Chesterfield, MO 63017
St. Mary's Health Center	St. Louis, MO 63117
Sarah Bush Lincoln Health Center	Mattoon, IL 61938
Southeast Missouri Hospital	Cape Girardeau, MO 63701
St. Luke's Hospital	Kansas City, MO 64111
St. Luke's South	Overland Park, KS 66213
St. Luke's East	Lee's Summit, MO 64086
St. Luke's North	Kansas City, MO 64154

TABLE 1. List of Testing Laboratories

Test	Performed by	Location	Details
Lot release testing, viability, CD34, TNC count, and Microbiology - SLCBB	St. Louis Cord Blood Bank	3662 Park Avenue, St. Louis, MO 63110	Testing Facility – CLIA certified
Lot release testing, viability, CD34, and TNC	St. Luke's Regional Lab	4401 Wornall Road, Kansas City, MO 64111	Testing Facility – CLIA #

Test	Performed by	Location	Details
count- SLCI			26D0652243
Microbiology-organism identification - SLCI	----------(b)(4)----------	----------(b)(4)----------	Testing Facility – Microbiology CLIA # ----------(b)(4)----------
Infectious Disease Markers - SLCBB	----------(b)(4)----------	----------(b)(4)----------	FDA registration # ----------(b)(4)---------- CLIA # ----------(b)(4)-----
Infectious Disease Markers – SLCI	----------(b)(4)----------	----------(b)(4)----------	FDA registration # ----------(b)(4)---------- CLIA # ----------(b)(4)-----
Human Leukocyte Antigen – SLCI and SLCBB	----(b)(4)-----	----------(b)(4)----------	FDA registration # ----------(b)(4)---------- CLIA # ----------(b)(4)----------
Hemoglobinopathy Testing– SLCI and SLCBB	----------(b)(4)----------	----------(b)(4)----------	Hemoglobin -----(b)(4)---------- CLIA # ----------(b)(4)----------

BACKGROUND/HISTORY

The St. Louis Cord Blood Bank (SLCBB) was established in 1995 as a joint effort of SSM Cardinal Glennon Children's Medical Center and the St. Louis University School of Medicine. The SLCBB submitted an Investigational New Drug application (IND 7183) in 1997 in order to nationally and internationally distribute their inventory of cord blood stem cells to restore hematopoiesis in unrelated donors. In preparation for the submission of this license application, SLCBB had a pre-BLA meeting in June of 2010 to receive guidance from the FDA.

Since the program's inception, over -(b)(4)- mothers have donated their cord blood to the SLCBB. Approximately -(b)(4)- units met their cord blood processing criteria and more than -(b)(4)- are currently available for transplantation. To date, nearly -(b)(4)- products have been distributed both domestically and internationally to treat patients with a variety of diseases and disorders.

The following recent changes have resulted in current SLCBB practices:

In November 2007, the use of ---(b)(4)--- was implemented in compliance with the National Cord Blood Inventory (NCBI) contract with the Health Resources and Services Administration (HRSA).

In January of 2008, the ----------(b)(4)----------.

In November 2009, after evaluating three processing techniques against the benchmark ---(b)(4)--- method, PrepaCyte-CB was selected as the system for manufacturing cord blood products.

In April 2010, they replaced the ----------(b)(4)---------- bag with the ----------(b)(4)---------- bag.

FACILITY DESCRIPTION: FLOOR DIAGRAMS

Floor diagrams were submitted for both the SLCBB and SLCI manufacturing sites. These diagrams included the locations of large pieces of equipment such as refrigerators, incubators, centrifuges, microscopes, and lab benches.

SLCBB floor plan

The SLCBB manufacturing facility is located on the first floor of the Pediatric Research Institute of the Cardinal Glennon Children's Medical Center. Security of the facility is maintained by a card access front entrance door, monitored by a 24 hour camera system, and guarded by CGCMC Security staff. There is only one entrance to the building that is accessible from the outside - other doors such as fire exits and those at the receiving dock are locked to the outside. Cameras are monitored by security at the hospital and the SLCBB resource coordinator. To further secure the inventory, cryopreservation areas are secured with card access doors at both entrances.

The SLCBB site is organized such that there are separate but adjacent rooms dedicated to Cord Blood Unit (CBU) qualification, characterization, processing, and cryopreservation.

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

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

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---(b)(4)---
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---(b)(4)---
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Reviewer Comment: *Based on our inspection of the St. Louis site, the locations of the various CBU processing tasks matched their description in the BLA submission. The processing rooms were adjacent to each other and there was not a lot of unrelated foot traffic in the area. The building seems to be designed appropriately for the task of processing and storing HPC, Cord Blood but there are numerous inspection issues cited on their 483 that remain unresolved. The need to resolve the outstanding 483 items will be a CR letter comment from DMPQ.*

St. Luke's floor plan

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

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

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---(b)(4)---
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Reviewer Comment: *The lack of a dedicated cell processing room raises some concerns about potential product contamination and there are numerous inspection issues cited on their 483 that remain unresolved. The need to resolve the outstanding 483 items will be a CR letter comment from DMPQ.*

HPC, CORD BLOOD DESCRIPTION

The final HPC, Cord Blood product consists of approximately 25 mls of cell suspension cryopreserved in 10% Dimethyl sulfoxide, and 1% Dextran 40. ----------(b)(4)---------- DMSO, (b)(4) Dextran 40, one vial per HPC, Cord Blood unit.

Cord blood collections are manipulated to reduce red cells and plasma using BioE's PrepaCyte-CB processing system. The final product is stored in an ----------(b)(4)---------- freezing bag and has -------(b)(4)------- segments attached to allow future analysis. The bag is enclosed in a protected ----------(b)(4)---------- and placed in an --------(b)(4)--------. HPC, Cord Blood units are frozen at a -----(b)(4)----- before being transferred into liquid nitrogen tanks (liquid phase) for long term storage. HPC, Cord Blood units are shipped to clinical sites in liquid nitrogen filled shipping containers.

The Proprietary Name: None at the time of this review. The applicant has proposed the name "AlloCORD" but has not yet submitted an appropriate Proprietary Name Request.

Non-proprietary Name: HPC, Cord Blood

Active ingredient: Cord Blood Hematopoietic Progenitor Cells
UNII Code : XU53VK93MC

Inactive ingredients:

Dimethyl sulfoxide 10%	UNII Code:	YOW8V9698H
1% Dextran 40 (Cryoserve)	UNII Code:	K3R6ZDH4DU

Therapeutic or Pharmacologic Class: Allogeneic cord blood hematopoietic progenitor cell therapy

Dosage Form: Injectable Suspension

NDC or ISBT code: SLCBB has stated verbally that they are planning on implementing ISBT 128 for labeling rather than use the NDC.

Reviewer Comment: *SLCBB has not submitted any information related to the use of ISBT 128. This will be a CR letter comment.*

CORD BLOOD COLLECTION

St. Louis Cord Blood Bank (SLCBB) has agreements with 29 hospitals in the metropolitan St. Louis region (includes eastern Missouri and southern Illinois). SLCBB has a contract with St. Luke's Cancer Institute (SLCI) in Kansas City, MO for collection and processing of cord blood units (contract manufacturing). SLCI has collection agreements with 4 hospitals in the Kansas City region.

Birth mothers interested in donation of cord blood may either contact the SLCBB or SLCI in advance or inform the physician/midwives/nurses at the delivery hospital. The information packet and a copy of the consent form are provided to the birth mother. The hospital staff witnesses the signing of the consent form prior to the delivery.

Collection Training

Trained obstetricians/midwives and nurses are responsible for pre-screening the birth mothers and perform the cord blood collection. The training program, which is managed by the cord blood bank nurse coordinator, includes a combination of grand rounds, small group meeting, office visits, and written informational packets. Training covers procedures for donor recruitment, pre-screening, consent, preparation of the cord to prevent contamination during collection and appropriate labeling. A copy of the training material has been submitted in the application. OBs/midwives responsible for collection of cord blood must sign a form acknowledging the understanding of the procedures. Yearly education is also provided with an accompanying test to ensure ongoing compliance. As part of the cord blood bank's quality assurance program, collectors are contacted when a contaminated cord unit is received by the bank. The contamination rate is tracked and additional education is provided when necessary. The labor and delivery nurses are trained on the collection procedure with a follow-up re-education on yearly basis. The collection hospitals are also visited by the cord blood bank nurse coordinator every 3 years to ensure compliance with the collection standards. During each visit, issues related to the collection, labeling and transportation are reviewed.

The SLCI facility uses the same training procedures.

Reviewer comment: *The training program for the collection staff is acceptable.*

Birth Mother Consent and Pre-screening

Birth mothers must sign an informed consent at the hospital prior to the delivery and/or active labor. The signing of the consent is witnessed by the labor and delivery nurse and the signed form is sent to the cord blood bank along with the collected unit.

The birth mothers are pre-screened by the trained labor and delivery staff and potential donors with any of the following findings are excluded:

- Multiple births

- Gestational age < 34 weeks
- Mother or father with history of cancer or blood disorder requiring chemotherapy
- Mother with history of an autoimmune disorder classified as severe
- Complicated deliveries or excessive maternal bleeding
- Malodorous placenta or amniotic fluid, or suspicion of chorioamnionitis
- Placental trauma or expulsion of placenta before or during collection

  Note: Refer to the Donor Eligibility section for additional pre-screening exclusion criteria related to risks for communicable disease.

If the above findings are discovered by the cord blood bank after collection, the cord blood unit is either discarded or used for research.

Cord blood collections are performed in-utero during vaginal or c-section deliveries by the trained OB/midwives and nurses in either the operating or the delivery room.

The SLCI facility uses the same pre-screening procedures.

Collection Controls

SLCBB and SLCI have established the following controls for the collection procedure:

- Collection supplies are packaged in individual boxes. The expiration dates of the supplies are listed on the outside of the collection boxes. The collection boxes have an assigned identification number which gets documented on the processing records when the unit is received at the processing laboratory.

  Note: SLCBB facility provides the pre-assembled collection boxes to the SLCI facility.

- Identity of the birth mother on the hospital label is verified against mother's hospital armband. The verification is documented on the Labor and Delivery Data form.

- To minimize risk of contamination, cross contamination or mix-up: 1) collections are performed in the delivery room by trained OBs/midwives, 2) single use, sterile collection bag and antiseptic swabs are used for collections and checked for expiration date, leakage and breakage , 3) venipuncture site on the cord is cleaned with ----(b)(4)---- prior to the collection, 4) collected unit is labeled with the hospital generated maternal label and information is confirmed by 2 individuals, 5) collection bag is placed in a biohazard bag and packaged in the individual collection box along with the maternal specimens and the associated paperwork.

- Relevant information such as delivery date and time, delivery physician identity, method of delivery, medication and blood transfusion at the time of delivery,

maternal pre-natal test results, delivery complications, baby's physical examination and any congenital anomalies are documented on the Labor and Delivery Data form.

Storage at the Collection Sites and Transportation

Individual collection boxes containing the collected units are stored at room temperature in a designated area in the hospital. Both SLCBB and SLCI have established agreements with designated couriers for transportation of cord blood units to the cord blood bank on daily basis at pre-scheduled pick-up times.

A. SLCBB transportation procedure (CL.17.08)

The courier service used by SLCBB is instructed to place collection boxes into a biohazard bag for transportation from the hospital to the cord bank. The vehicle is equipped with a digital thermometer. The driver documents the date, time, and the temperature reading in the vehicle at each pick-up stop and at the time of delivery to SLCBB. The acceptable temperature during transportation is (b)(4).

If the delivery is after cord bank's business hours, the biohazard bag containing the collection boxes and the associated delivery documentation are placed in a designated locker for temporary storage. The locker is equipped with a temperature data logger (temperature -(b)(4)-). The units are removed from the locker each morning by the processing laboratory staff. The data logger temperature reading is reviewed every other month. For any identified temperature excursion, a retrospective investigation is conducted by evaluating the viability and potency of the affected products.

Reviewer note:

- *During the 2/22/12 teleconference, the reviewer expressed concern that the appropriate temperature is not maintained throughout shipping. In the 6/26/12 submission (SN10, amendment 9), the applicant explains that the maximum transport time is about -(b)(4)- and for most pick-up runs, the time between temperature recordings is about ---(b)(4)---. The applicant also submitted an audit report (QM.11B.03, 9/15/11) that concludes the maximum time without any temperature recording is about ---(b)(4)---.*
- *The transportation SOP does not specify whether units are discarded if the temperature is outside the acceptable range.*

Reviewer Comment:

The reviewer does not feel that the current procedures are adequate to ensure the temperature is monitored and maintained. The reviewer recommends that a data logger be used for recording of the temperature during transportation. In addition, the shipping SOP needs to be revised. The SOP should also specify whether the units are discarded if the temperature during transportation or temporary storage is not within the acceptable range. A CR letter comment related to this issue has been included.

In teleconference on 7/11/12, the reviewer communicated this recommendation to the applicant, but it has not been addressed.

B. SLCI transportation procedure (SLCI-CTS 4039.01)

The courier service used by SLCI, places the individual collection boxes in a qualified transport cooler that is equipped with a thermometer to monitor the temperature during transportation. The acceptable temperature during transportation is (b)(4).

Reviewer comments:

- *It is not clear whether the transport cooler is equipped with a thermometer that simply displays the temperature or a logging thermometer that records the temperature. The applicant needs to provide clarification.*
- *The SLCI SOP states that upon receipt of units, the processing laboratory staff verifies the temperature and documents any extreme variations which **may** result in product discard. However, the SOP should clearly establish the conditions under which the units are discarded if the transportation temperature is outside the acceptable range and it should not be a subjective decision.*
  A CR letter comment related to this issue has been included.

Note: refer to the collection validation section regarding transportation validation.

Pall Collection Bag Qualification

Cord blood is collected in single use, sterile collection bags containing (b)(4) CPD ------(b)(4)------. In April 2010, the ----------(b)(4)---------- which is FDA NDA approved.

Prior to implementation of the ---(b)(4)--- bags, total of (b)(4) bags were evaluated for the following (Report: QM:01.12.01A):

- Verification of the tare weight provided by the bag manufacturer: Empty bag weight (b)(4) + CPD volume (b)(4)
- Bag integrity check

- ----------

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

----------.

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

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

Results:
- ----------(b)(4)----------
  ----------.
- ----------
  ----------(b)(4)----------
  ----------.
- ----------(b)(4)----------

Collection Procedure Validation

For collection validation, the applicant has submitted a publication from 1997 (The Journal of Maternal-Fetal Medicine 6:320-323). The purpose of the study was to evaluate the feasibility of an obstetrician-based cord blood collection model. Over 200 physicians and 40 area obstetrical units were trained on the collection of cord blood during the 3rd stage of labor (in-utero collections). A total of 293 bankable products collected by the OBs were compared to 41 units collected post-delivery by trained technicians (ex-utero collections). For this study, the minimum acceptance criteria for the collected units were volume $\geq$40ml and TNC >$7x10^8$. Collected units were processed using the manual centrifugation using Hespan. Cord blood volume, TNC and total CFU were evaluated.

TABLE 2. Comparison of banked 3rd stage collections with post-delivery

	Post-delivery collections (n=41)	3rd stage collections (n=293)
Cord blood volume (ml)	75 (range 41-140)	81 (range 40-170)
TNC ($x10^8$)	10.4 ± 5	11.7 ± 4.8
Total CFU ($x10^5$)	16.6 ± 13	9.8 ± 5.2

Reviewer comments: *It is not clear whether the TNC and CFU values listed in the above table are pre or post-processing.*

Study conclusion: The applicant cited an article which generally showed that there was no significant difference between the two collection models with respect to the cord blood volume or TNC. Over 50% of the collected units were not banked due to low volume or TNC or other issues related to transportation, labeling, etc. Based on the

results of the study, the applicant determined that the OB collection model could be implemented.

Reviewer comment:
The above study provides supporting data demonstrating that the OB collection model is feasible. However, the applicant has since changed several practices and procedures, e.g. collection bags, processing methods, unit's minimum acceptance criteria, donor screening. In the 2/22/12 teleconference, the applicant was asked to submit a validation summary that covers all aspects of collection procedures that are currently in use (e.g. completion of donor screening documentation, labeling, collection volume, and transportation) with pre-defined acceptance criteria. The applicant was also informed that the validation should be performed at both facilities. A CR letter comment related to this issue has been included.

The applicant provided a draft validation plan via email on 7/6/12. The reviewer suggested revisions to the applicant in a teleconference on 7/11/12. However, a final validation plan was not received or reviewed.

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). The unique identification barcode label is assigned to the cord blood unit and the maternal specimens at the cord blood bank. The unique identification numbers are generated by a program named --------(b)(4)----------. The numbering system starts with the prefix "SL" followed by 6 digits (SLxxxxxx). The identical number that is assigned to the maternal specimens ends with the letter "M" (SLxxxxxxM).

To establish linkage between the birth mother and the collected cord blood unit, the unique donor identification number is applied to all the maternal documentation (e.g. consent, medical and family history questionnaires), blood samples and all the associated testing and processing forms. The unique donor identifier is also included on the Comprehensive Matched Cord Blood Report provided to the transplant centers.

Reviewer comment*: The applicant has not provided information regarding the unique donor identification used at the SLCI facility. A CR letter comment related to this issue has been included.*

CORD BLOOD PROCESSING

Overview

Processing of CBUs can occur at either Saint Luke's Hospital of Kansas City MO, or at the Cardinal Glennon Children's Medical Center in St. Louis MO. Standard Operating Procedures (SOPs) were only submitted for the St. Louis manufacturing facility, but in the submission it was indicated that the Kansas City site also manufactures using the

same SOPs. CBUs processed at Saint Luke's Hospital are lot release tested and cryopreserved prior to shipment to St. Louis for long term storage. The SLCBB reviews all Saint Luke's batch records for product safety, purity, and potency prior to approval for transport to the SLCBB site for long term storage.

Cord blood collections are transported to the processing facility via contracted courier seven days a week. Following evaluation of labeling, adequacy of maternal samples, cord blood appearance, and CBU volume and cell content, the cord blood collections are manipulated to reduce red cells and plasma using BioE's PrepaCyte-CB processing system. The final product is contained in an ----------(b)(4)---------- bag to which a volume of cryoprotectant solution resulting in 10% final Dimethyl sulfoxide (DMSO) concentration is added. The bag is protected from cross contamination using ----------(b)(4)----------, placed in an -------(b)(4)-------, and frozen at a -----(b)(4)------ before being transferred into liquid nitrogen for long term storage.

Each manufactured product has a batch record (product file) in which all source documents are stored. The batch record includes the results of potency (nucleated cell, CD34, colony forming unit, viability), safety (microbial surveillance and hemoglobinopathy screening), and identity (human leukocyte antigen (HLA) and ABO/Rh) testing. After the batch record is reviewed by the SLCBB's Quality Specialist, HPC, Cord Blood units are placed in inventory.

Reviewer comment: *Review of the batch records during inspection led to a 483 observation because the current batch records were not detailed enough and did not document the performance of critical steps. This issue will be addressed by DMPQ.*

Initial Cord Blood Qualification

Each cord blood unit arrives from the collection center labeled with identifiers that include mother's name, collection center, date of birth, address, and record number. Identifiers on all components within the collection box are compared prior to the start of processing. The unique identifier is entered into the Collection Log Book and labor and delivery forms are time/date stamped.

Each CBU collection received is assigned a unique alpha-numeric identifier which allows product tracking throughout its existence. Barcode labels are affixed to the collection bag, maternal blood samples, the donor's paperwork, and the individual cord blood unit processing tray.

The initial qualification criteria include the following:

- Verification of donor identity on the cord blood unit collection bag, maternal specimens and associated paperwork.
- Visual inspection of the cord blood container for integrity, obvious sign of contamination and presence of clots

- Pre-processing cord blood volume (b)(4)
- Pre-processing TNC ---(b)(4)---

The weight of the Cord Blood collection must be at least --------(b)(4)------- before total nucleated cell (TNC) determination and further processing. The Weight/Volume of the Cord Blood collection is calculated by subtracting ----------(b)(4)---------- bag) from the total bag weight.

A (b)(4) number, currently about (b)(4) of the CBUs received, do not get processed because they do not make weight, or do not meet donor eligibility requirements.

If there is an excess of CBUs available for processing, some CBUs may be stored ----------(b)(4)----------. SLCBB documents the time between collection and processing, including if cells are -----(b)(4)------, in the batch record. To be processed, CBUs must be received within -(b)(4)- of harvest and frozen within --(b)(4)-- of collection (TE.01.03).

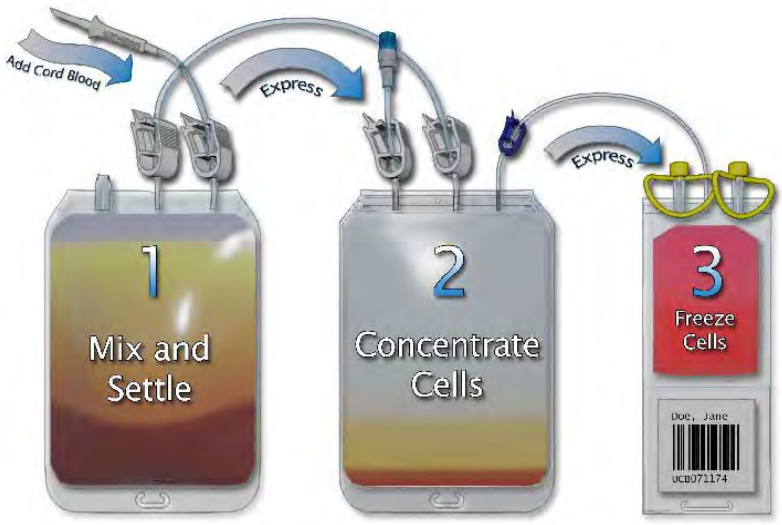
The SLCI facility uses the same qualification criteria as the SLCBB facility.

Reviewer comment: *In SOP TE.01.03 (Unrelated Umbilical Cord Blood Processing Using PrepaCyte-CB), it is stated that if a collection from a single donor is received in ---(b)(4)--- and the total volume is less than ----------(b)(4)---------- (step 9). The collection procedure (SOP CL.06.07) doesn't describe collections into -(b)(4)-. This is a CR letter comment.*

PrepaCyte-CB processing of cord blood

The PrepaCyte-CB kit is a functionally closed WBC enrichment system in which cord blood is depleted of red blood cells (RBCs) and plasma. The PrepaCyte-CB kit has been cleared via 510(k) (BK070067) and is also the subject of MF (b)(4). The kit consists of three interconnected bags (Figure 1). Bag 1 contains 150 mL of the PrepaCyte-CB reagent that causes cord blood red blood cells to aggregate out of solution under normal gravity conditions. Bag 2 of the kit is used to concentrate the WBCs and Bag 3 is used for cryopreservation. The PrepaCyte-CB reagent contains Dextran (500,000 kd) which decreases the zeta potential of RBCs, enhancing sedimentation of the RBCs by rouleaux formation (formation of stacks of RBCs). According to the 510(k) submission, the mechanism of action is the same as ----------(b)(4)----------. The formulation for one liter of the separation media consists of (b)(4) of Dextran, ----------(b)(4)---------- Human Serum Albumin, ----------(b)(4)---------- and water.

FIGURE 1. Diagram of PrepaCyte-CB kit



CBU Processing and Sampling (SOP TE.01.03)

(b)(4)

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

---.

1 page redacted (b)(4)

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

(b)(4)

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

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

Reviewer comments:

- *The removal of the concentrated WBCs using the ----(b)(4)---- to allow the accurate volume measurement is a deviation from Figure 1.*

- *During inspections, we observed that SLCBB and SLCI had (b)(4) cord blood units processed simultaneously in a single -----(b)(4)----- during the mixing of the CBU*

with the PrepaCyte-CB reagent, RBC settling, and plasma expression. This was cited as an unacceptable practice during the inspection.

Cord blood cryopreservation

The ----------(b)(4)---------- (used in CBU Processing and Sampling (b)(4) described in previous section) is a sterile ----------(b)(4)---------- DMSO, (b)(4) Dextran 40 (TE.11.16). The amount of this mix added to the product is determined by calculating the amount of this mix needed to be added to have 10% DMSO in the final product. The purpose of the Dextran 40 (average mol. wt. 40,000) is to enhance blood flow, particularly in the microcirculation.

The ----------(b)(4)---------- into the freezing bag with --(b)(4)--. The bag and -------(b)(4)-------- to enclose the bag and the segments. The bag is marked at the points where the segments are sealed. The freezing bag is then placed in the -------(b)(4)------ which is also ----(b)(4)----, and this assembly is placed into a metal cryopreservation cassette.

A ------(b)(4)------ freezer is used to freeze the cord blood units to (b)(4). Probes are used to document the integrity and rate (--------(b)(4)---------) of the freezing process. They also describe a passive procedure where the bags are place in a (b)(4) freezer. The passive procedure is used as a back-up system if all the -----(b)(4)------ freezers are broken.

Storage of HPC, Cord Blood

After freezing, the HPC, Cord Blood units are placed in liquid N2 and transferred to the large long term liquid nitrogen tanks (TE.09.01). The ---------(b)(4)-------- and placed in the vapor while the units are transferred to numbered racks.

Freezers are located in secure areas and can be accessed only by authorized personnel. The cassettes are placed in ----------(b)(4)---------- liquid nitrogen freezers. The products are submerged in liquid N2. The tanks are automatically filled and levels are monitored by a ---(b)(4)---.

The cassettes are placed in assigned storage locations and tracked by freezer number, rack, and frame position. The locations of the HPC, Cord Blood units are entered into a searchable database.

HPC, CORD BLOOD RELEASE TO TRANSPLANT CENTERS

When a unit is requested for transplant, a checklist is placed in the product file to document confirmatory test results, verification and evaluation of collection documents, sample distribution, search activity, and export approval. The Quality Specialist reviews donor eligibility, and lot release data, and makes a determination of the unit's availability for distribution. The SLCBB nursing staff performs a follow-up phone call with the maternal donor if the last date of donor contact is greater than 6 months ago.

One segment (--------(b)(4)---------) is thawed for the confirmatory test procedure. Approximately (b)(4) are used for viability testing (------(b)(4)--------), (b)(4) are used for a CFU assay, and the remaining sample is spotted onto HLA cards.

HLA typing will be done by --(b)(4)-- unless the request for the unit sample came from NMDP, then the testing will be done by ----------(b)(4)---------. A maternal sample will also be sent for HLA retesting to confirm that unit and mother share a haplotype. Cord serum or plasma will be sent for CMV testing if the maternal blood sample was positive for CMV ---(b)(4)---. Potency testing is performed on the segment by measuring colony forming units and viability by ----------(b)(4)---------- assay. Confirmatory test results are entered into ------(b)(4)-------.

Once testing is completed, a final review of the product file is performed by the SLCBB quality control analyst and medical director/designee. If approved, the product is then available for shipping and the transplant center can request a unit for use in clinical application. Before the HPC, Cord Blood is shipped, the transplant center needs to send a copy of the signed consent form, agreement to thaw procedure, and agreement to complete and submit follow-up forms.

CORD BLOOD PROCESSING VALIDATION

The BLA submission did not contain a processing validation study. The only information presented was data from studies comparing the PrepaCyte-CB kit to other processing methods including the previously used "------(b)(4)--------". These data could be useful in establishing acceptance criteria for a future validation study.

Selection of PrepaCyte-CB (BioE) for CBU processing

In appendix R SLCBB describes the evaluation of (b)(4) technologies for use in reducing the volume and red blood cell count of cord blood collections. The (b)(4) technologies studied were PrepaCyte-CB, -----(b)(4)-----. A minimum of (b)(4) units were processed using each method and results were compared to the ---(b)(4)--- method that uses ----------(b)(4)----------. The evaluation period began on January 12, 2009.

The efficiency of CBU processing and recovery after cryopreservation was evaluated for TNC recovery, MNC recovery, CD34 enumeration, CFU assay, viability using ----------(b)(4)----------, and Sterility. In addition, thawed segments were assayed by CFU assay and viability using -----(b)(4)-----.

SLCBB concluded that the PrepaCyte-CB kit provided the best cost versus performance alternative and has proceeded to use this method since November, 2009.

Reviewer comment: *The PrepaCyte-CB kit performed as well as, or better than, the other CBU processing kits with the exception of the Post-Thaw (b)(4) viability results. There*

was no explanation for the (b)(4) difference between the (b)(4) viability obtained with the (b)(4) kit and the (b)(4) viability obtained with the PrepaCyte-CB kit.

In appendix S SLCBB describes an investigational trial to further assess the PrepaCyte-CB kit for a period of ----------(b)(4)----------. The data collected were compared to data from units processed with the ----------(b)(4)---------- method they were previously using.

TABLE 3. Comparison of PrepaCyte-CB to (b)(4) method

---(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 Post TNC count, CD34+, viability, and CFU counts were all well above the acceptance criteria outlined in the Cord Blood Guidance. Note, the recovery of White Blood Cells was increased from (b)(4) to (b)(4) when the PrepaCyte-CB kit was used.*

SLCBB also collected data on the cell recovery from their freeze-thaw process (SOPs SE 04.04 and SE 05.10) as shown below. In later studies, these data will be referred to as "Control data".

TABLE 4. PrepaCyte-CB Thaw Control Group – Median Recovery Data

(b)(4)

TABLE 5. ---------(b)(4)--------- comparison data

(b)(4)

Reviewer comments:

- *The PrepaCyte-CB processing results in significantly smaller numbers of red blood cells.*
- *These assessment studies were not set up as a "Validation" study. The results show that the PrepaCyte-CB kit performs as well as or better than the ----------(b)(4)---------- method. These results may be useful in establishing acceptance criteria for future validation studies. Current SOPs were not used to process the units.*

Additional validation information

During the site inspection, SLCBB presented a new manufacturing validation plan and data for review and comment. This information has not been formally submitted to FDA in the BLA or in an amendment.

In this validation plan, 3 CBUs were retrospectively selected and then used to validate the thawing and infusion preparation procedures. Confirmatory HLA and CFU testing performed on attached segments were deemed acceptable and the units were shipped to the Kansas City site and back in dry shippers. The CBUs were then thawed and reconstituted. Analysis of viability, CFU, CD34+ cell count, TNC, and percent recovery were all deemed acceptable based on their values relative to their control group.

Reviewer Comments:

Regarding Process Validation:

- *The use of retrospectively selected CBUs for the validation of the PrepaCyte-CB kit is unacceptable. Processing validation must be performed prospectively using the current SOPPs.*
- *During inspection there was an observation that cited an inadequate segregation of CBU units during processing. Specifically, (b)(4) HPC, Cord Blood units were being processed concurrently by -----(b)(4)----- in a ----------(b)(4)----------. To address this observation, significant changes in the cord blood processing SOP will need to be made. The validation of the cord blood processing should be done after the implementation of these changes.*
- *SLCBB recently submitted new collection and processing validation plans by email for comment. FDA supplied suggested modifications to the validation plans on 7/11/2012.*

A CR letter comment related to process validation has been included. Note that process validation needs to be performed for both the SLCI and SLCBB manufacturing sites.

Regarding thawing and reconstitution:

- *The validation data for the thaw-shipping-reconstitution procedure was similar to their historical control group (TABLE 4). However, pre-specified acceptance criteria were not identified in their validation plan.*

A CR letter comment related to thawing and reconstitution has been included.

FREEZING PROTOCOL VALIDATION

-----(b)(4)----- consisting of (b)(4) DMSO and (b)(4) Dextran 40, both USP grade, is used as a cryoprotectant. -------(b)(4)--------- is sterilized and meets USP standards for labeling as sterile and endotoxin free. It is packaged in ----------(b)(4)----------. The cryopreservative constitutes (b)(4) of the final volume.

They used (b)(4) CBUs processed using the Prepacyte-CB kit to validate the freezing process using the ---(b)(4)--- solution in conjunction with the -----(b)(4)------ freezer (Appendix I – June 2011). After freezing, the units were stored in liquid nitrogen tanks for ---(b)(4)--- and then reconstituted. The control group used for comparison, were (b)(4) CBUs that had been prepared using the PrepaCyte-CB kit and then cryopreserved in an ----------(b)(4)---------- DMSO and (b)(4) Dextran 40.

Data: They measured a mean post thaw viability of (b)(4) for cells cryopreserved in -------(b)(4)--------- compared to (b)(4) in their control group (TABLE 4). Total viable CD34+ cells were only recovered at an average of (b)(4) compared to the control group's (b)(4) (TABLE 4). The mean TNC and WBC recovery was (b)(4) compared to (b)(4) for the control group.

Reviewer comment: *The post-thaw results for viability and TNC recovery were superior to their control group data and the CD34 recovery was within one standard deviation of the control group result. However, the validation plan did not contain clearly specified acceptance criteria. During our 7/11/2012 telecon, SLCBB was informed that they need to include the freeze-thaw process in the validation study they are preparing to perform. This review issue is part of the PrepaCyte-CB processing validation and is addressed in the PrepaCyte-CB CR letter comment.*

They have also qualified a -----(b)(4)------ freeze protocol, to use as a back-up in case the --------(b)(4)-------- freezing equipment has operational issues (Appendix P – December 2010). The storage cassettes containing the CBUs were placed within insulating material in a (b)(4) freezer -(b)(4)-. They monitored the freeze process with a probe and found that it took about (b)(4) to reach (b)(4). The mean viability in (b)(4) samples measured by ---(b)(4) averaged (b)(4) (compared to (b)(4) in Control Group, Table 4), while viability using (b)(4) only averaged (b)(4) (compared to (b)(4) in Control Group). TNC recovery and CD34+ cell recovery were greater than control data.

Reviewer comment: *Using the backup freezer in an emergency situation is acceptable.*

SHIPPING AND SHIPPING VALIDATION

Shipping – reference SN03 (received 12/13/2011)

The SLCBB distribution procedure, SOP SE.02.07, describes the charging and labeling of the shipper, packing of the HPC, Cord Blood, temperature monitoring of the interior of the shipper with a probe, and weighing of the shipper. The following documents are shipped with the HPC, Cord Blood:

a. Notification of Shipment
b. NMDP Product insert (for NMDP shipments)
c. Receipt instructions
d. Comprehensive matched cord blood report
e. Copy of patient and unit confirmatory testing results
f. Blank cord blood thaw form
g. Thawing and reconstitution procedures
h. Follow up forms
i. Circular of information

***Reviewer's Note**: This list does not include the Prescribing Information, which will need to be provided with each HPC, Cord Blood shipment, and the PI should include the thawing instruction. This also relates to the thawing and reconstitution comment above and is part of the larger issue that is addressed in a CR letter comment.*

SLCBB uses liquid nitrogen dry shippers for the transport of cord blood units to transplant centers. The shippers are designed to maintain a temperature of -(b)(4)- or colder for ----(b)(4)---- LN2 containers) or -----(b)(4)----- containers). SLCBB has assigned the permissible time limit of ----(b)(4)----. The temperature is monitored throughout the transport by a data logger that is analyzed when the shipper is returned to SLCBB.

Dry shipper validation

The dry shippers are re-qualified each time they are returned to SLCBB. The vessel is filled with liquid N2 and then the temperature and weight of the container are monitored. If they hold temperature for ---(b)(4)--- container) or ---(b)(4)--- container) they are tagged ready to be used for shipping. Each shipper has its own notebook where the temperature logs and shipping history are maintained.

***Reviewer Comment:** During the inspection, notebooks containing data for individual shippers were examined. The notebooks documented the delivery site, delivery time, contained the temperature log, documented any temperature deviations, and documented recharging and requalification, if necessary. The validation data are sufficient for qualifying the shippers.*

Evaluation of the effect shipping has on product – reference SN03 (received 12/13/11)

When transplant centers receive HPC, Cord Blood they usually analyze an aliquot of the reconstituted product to determine TNC count and viability. SLCBB submitted data collected from the clinical centers to help demonstrate that shipping did not have a detrimental effect on the product. The aggregate ---(b)(4)--- viability and TNC recovery data from the clinical sites were similar to the control data collected from CBUs that did not undergo shipping.

Reviewer comment: *Although this data did not provide information related to individual units, it is consistent with the shipping process not having a systemic detrimental effect on product quality, and supports the dry shipper validation.*

Transfer of CBUs from SLCI to SLCBB

Lot release data from CBUs processed and cryopreserved at the St Luke facility are evaluated by their director to identify those that appear eligible for transfer to the St. Louis Cord Blood bank (SLCBB). Excel spreadsheets for batches of (b)(4) CBUs are sent for review and consideration for transfer to SLCBB. Upon receiving the list of approved CBUs from SLCBB, the following documentation is prepared to track the shipment of the CBUs:

1) Shipping of preserved product Worksheet
2) Release of Umbilical Cord Blood Units from Storage Documentation
3) Aliquot and Archive Log Sheet
4) Cord Transfer Log

The CBUs are shipped in a liquid nitrogen cryoshipper with data logger. Cord and maternal spot cards are shipped in a specimen bag, aliquots of plasma, and precipitated red blood cells are shipped on dry ice.

Transport from SLCI to SLCBB – Validation

Cryopreserved units processed at the SLCI were evaluated for inclusion into listed inventory. (b)(4) units that were processed using the old "---(b)(4)---" method between --------(b)(4)-------- were randomly selected for post-thaw evaluation. The units were thawed according to the reconstitution method and compared to (b)(4) control samples that were processed at SLCBB (reference SN03 - received 12/13/11).

The (b)(4) viability and CD34+ viability were (b)(4) than the SLCBB group, the CFU and TB viability numbers were ----------(b)(4)----------, and the TNC recovery was (b)(4) for cells shipped from the SLCI site.

Reviewer Comment: *The data provided was consistent with the shipping process not having a detrimental effect on product quality.*

METHODS FOR PREPARING HPC, CORD BLOOD FOR INFUSION

Reconstitution Dilution Method (SOP SE 04.04)

Reconstitution is performed at the clinical site. After confirming product identity the CBU is submerged in a 37°C water bath. The reconstitution solution is prepared by combining 250 mls of 10% Dextran 40 (low molecular weight dextran) with 50 mls of 25% albumin. 50 mls are mixed with the CBU and then a 1 ml aliquot is taken for nucleated cell count, CD34+ count, viability, CFU assay, ABO/Rh confirmation, microbial cultures.

Wash Method (SOP SE 05.10)

At the clinical site, after confirming product identity the CBU is submerged in a 37°C water bath. The wash solution is prepared by combining 250 mls of 10% Dextran 40 (low molecular weight dextran) with 50 mls of 25% albumin. 50 mls are mixed with the CBU and then the cells are transferred to a bag for centrifugation. After 20 minutes at 650g, 75% of the wash solution is expressed out of the bag. A 1 ml aliquot is taken for nucleated cell count, CD34+ count, viability, CFU assay, ABO/Rh confirmation, microbial cultures.

Emergency product recovery

When the cell containing bag is thawed in the water bath, it is placed inside another sterile bag. If a leak is detected then the contents are transferred to another transfer bag (SOPs 05.10 and 04.04).

Validation of Methods for preparing HPC, Cord Blood for infusion

SLCBB stated in SOPs 05.10 and 04.04 that multi center data has resulted in a mean TNC recovery of (b)(4) and viability of (b)(4) for both the reconstitution dilution and wash methods. SLCBB infusion instructions state that the cells should be infused as soon as possible, less than four hours after the start of the thawing procedure.

Reviewer comments:

- *Historical data from clinical sites is informative but it does not constitute a traditional validation study since acceptance criteria and sample size are not predefined. Reconstitution data for units that have been prepared using the most current PrepaCyte-CB processing SOPs is needed. Additional validation data should be submitted with the PrepaCyte-CB processing validation study. During our 7/11/2012 telecon, SLCBB was informed that they need to include the CBU reconstitution process in the validation study they are preparing to perform. This review issue also relates to the thawing and reconstitution CR letter comment referenced above..*

- *The recommendation of infusing the cells as soon as possible is acceptable.*

STABILITY

Stability of Cryopreserved CBUs

SLCBB performed multiple studies to determine the stability of HPC, Cord Blood units cryopreserved between 1996 and 2009. They analyzed thawed units to determine if sterility and potency were maintained for up to 15 years. Note that CBUs from this time period were prepared using the ---(b)(4)---- method rather than the current PrepaCyte-CB method.

SLCBB has also submitted stability data from CBUs that have been processed using the PrepaCyte-CB method during the past 3 years.

Stability of Sterility

SLCBB has thawed (b)(4) cryopreserved sterile products stored up to 15 years and (b)(4) were negative for post-thaw growth. They suspect pre-cryopreservation --(b)(4)-- problems caused the (b)(4) positives. They have received (b)(4) reports from transplant centers and have received (b)(4) reports of contamination. They suggest that these could be caused by pre-infusion steps at the transplant centers.

Reviewer Comment: *Product sterility would not be expected to be affected by storage in liquid nitrogen unless there is a failure in container closure/integrity.*

Stability of potency

Since 2001, CBU segment potency has been evaluated by -----(b)(4)----- viability and colony forming unit assay. Acceptable limits are a CFU recovery (b)(4) compared to post-processing CFU and / or CFU/TNC ratio -(b)(4)-.

A stability study was performed to evaluate the post thaw potency for (b)(4) CBUs cryopreserved between 1996 and 2009. Post thaw recoveries and viability are provided in Table 29 of their original submission and in TABLE 7 below.

(b)(4)

SLCBB also submitted another set of data (from table 45 of the original submission, TABLE 8 below) that compared age of the cord blood unit to the TNC recovery, post thaw viability, and cell dose.

(b)(4)

(b)(4)

Reviewer Comment: *Aggregate product potency does not appear to be negatively impacted by prolonged time in storage, suggesting that the CBUs are stable when stored in liquid N2 for the time period studied – up to 15 years. However, these studies do not*

include data from individual units, so it is impossible to determine if individual units are losing potency.

Note these studies were done on units that were processed with the ---(b)(4)--- method.

Stability of CBUs prepared using the PrepaCyte-CB kit

Units are currently manufactured with PrepaCyte-CB. This processing change occurred on 11/3/2009. To date, (b)(4) units have been exported for use in transplant from this population.

TABLE 9. Stability data for CBUs processed using PrepaCyte-CB

(b)(4)

(b)(4)

Reviewer Comment: *The aggregate data suggests that the CBUs manufactured using the Prepacyte-CB kit are stable for the time period studied, up to (b)(4). However, these*

studies do not include data from individual units, so it is impossible to determine if individual units are losing potency.

To establish an expiration date, SLCBB needs to develop a stability plan with predefined acceptance criteria that measures the length of time that the licensed units made using the PrepaCyte-CB process are stable. This will be a CR letter comment.

SLCBB QUALITY UNIT

SLCBB stated that their Quality Unit has the following responsibilities:

1) Review of all batch records
2) Approval of all cord blood units for availability and export
3) Approval of all validation/qualification plans, including sampling plans, test procedures, specifications and control mechanisms
4) Approval/rejection of procedures affecting identity, strength, quality and purity of the HPC, Cord Blood units
5) Document control
6) Approval/rejection of all components, containers, closures, packaging, labeling
7) Assure compliance with written SOPs
8) Investigation of complaints, adverse events, deviations, errors, occurrences and reporting of these events if indicated
9) Conducting internal audits, including formulation of corrective action and monitoring the effectiveness of the actions

These activities are performed by the Quality Control Section, the Quality Committee and the Quality Specialist. The Quality Committee at the SLCBB consists of the following individuals:

Quality Specialist
Medical Director
Executive Director
Laboratory/Scientific Director
Biostatistician
Search and Export Coordinator
Collections/Donor Eligibility Coordinator

The SLCBB Quality Control Section was formally incorporated at the SLCBB as of August 1, 2011. It is comprised of a Senior Technologist, a Technologist, and the Laboratory Director. The Quality Control Section is responsible for establishing:

1) Daily preventative maintenance for the manufacturing equipment
2) Equipment specifications for ordering purposes, qualification and approval, and developing maintenance schedules
3) A reagent conformance program for Critical Reagents & Supplies
4) Formal training and Proficiency Testing for manufacturing

Reviewer Comment: *This quality control system appears to be designed adequately to control the manufacturing process and product quality. However, a 483 observation from the inspection stated 'Documented evidence is lacking to demonstrate the Quality Control Unit (QCU) performs all of their defined roles and responsibilities included in SOP QM.02.03.' The need to resolve the outstanding 483 items will be a CR letter comment from DMPQ.*

LABELING AND TRACKING

In-Process Labeling

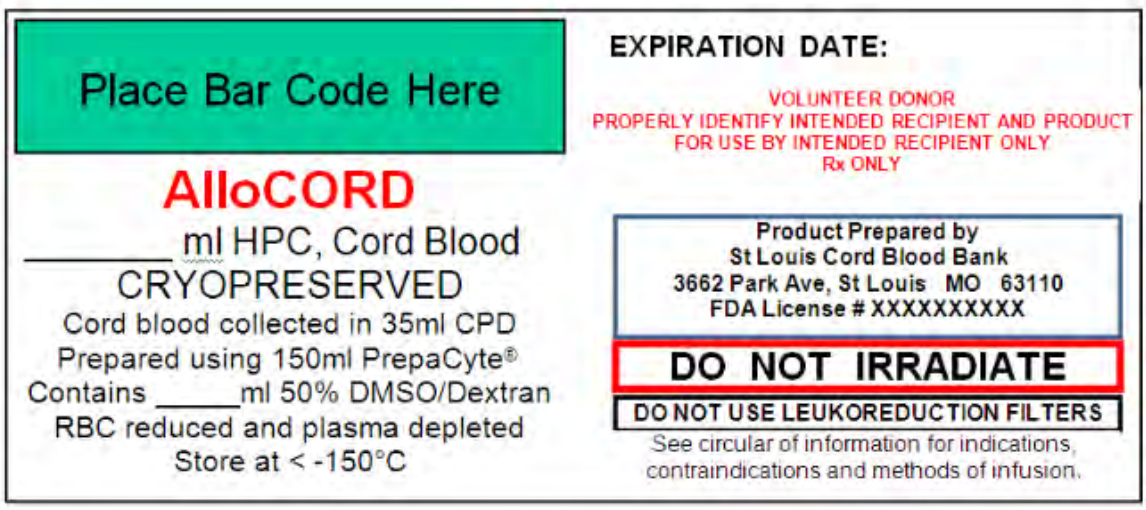
Identifiers on all components in the processing box include mother's name and specific form of identification used by the collection center, which could be date of birth, address, record number.

After the CBUs are weighed, Barcodes are assigned, prepared, and attached to the collection bag and the maternal samples. (b)(4) labels are generated to label all the samples created during subsequent processing steps. The identifiers and unique alpha/numeric identifier are entered into the Collection Log Book. The Labor and Delivery Form are time stamped.

Product labeling

SLCBB submitted a proposed label (Figure 2), shown below, to be affixed to the cryobags of HPC, Cord Blood and stated that it was designed per FDA's Guidance: Labeling for Human Prescription Drug and Biological Products.

FIGURE 2. Proposed label



SLCBB has indicated that they plan to implement ISBT (International Society of Blood Transfusion) 128 labeling. However, no documentation related to the use of this standard has been submitted to the BLA. Because of this planned change to the content and format of the cryobag label, the review team will not provide specific comments on the draft submitted to the BLA original submission.

Reviewer Comment:
As mentioned previously, the sponsor communicated the intent to switch to ISBT 128, but has not yet done so. This will be addressed in the CR letter.

The sponsor has proposed a proprietary name and a proprietary name request will need to be made and approved before it can be included in the labeling. We will inform the sponsor of the need for approval of their proprietary name request in the CR letter.

RETENTION SAMPLES

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

---.

Reviewer Comment: *----(b)(4)---- may be available for use as a retention sample, but SLCBB has not been willing to commit to this. Therefore the current proposal does not meet the regulatory requirement for a retention sample. A CR letter comment on this issue is recommended.*

REAGENTS USED IN MANUFACTURE

Material Acceptance, Release and Conformance Testing Policy (page 81 of BLA submission)

The SLCBB performs vendor qualification followed by an initial reagent validation. Initial reagent validation confirms that the provided material meets written specifications described in the SLCBB SOPs to qualify the reagent or material for use.

Each received lot undergoes an initial assessment and release testing to qualify the supplied material for use in manufacturing.

Conformance Testing of Critical Reagents and Supplies

For the purpose of testing, the SLCBB has classified materials into critical and non-critical components. Criticality is assigned to components based on direct contact with the cord blood product or a requirement for special handling.

Other than the Prepacyte Reagent, the cryoprotectant is the only reagent that is added during the processing of the CBU. SOP TE.11.16, describes the preparation and use of a cryoprotectant consisting of a mixture of DMSO and low molecular weight dextran (LMD) in dextrose.

Currently, SLCBB is using a sterile ----------(b)(4)---------- containing (b)(4) DMSO and (b)(4) Dextran 40 (----------(b)(4)----------) However, SLCBB also proposes to have an --------(b)(4)-------- of cryoprotectant that is a ----------(b)(4)----------. The (b)(4) mixture of DMSO and Dextran results in an equivalent (b)(4) DMSO (b)(4) Dextran 40 freezing solution.

All critical components that contact the cord blood are tested for sterility. They state that additional testing of at least one key characteristic of a critical reagent is performed to ensure that the product matches the COA.

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

Reviewer comment: *SLCBB should specify the frequency they plan to monitor the critical reagent attributes, and supply representative data from their analyses. This request will be communicated as an information request prior to a potential resubmission.*

CONTAINER CLOSURE SYSTEM AND LEACHABLES

Bag systems have been evaluated for sterility, burst testing, clamp function, and ability to withstand freeze/thaw (cryopreservation bags).

Collection Bag

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

PrepaCyte-CB Processing Kit

Cord blood collections are processed using the ---(b)(4)--- PrepaCyte-CB reagent kit (BioE, 510(k) cleared, BK070067) to harvest stem cells by isolating the white blood cell fraction of whole cord blood.

Freezer Bag (part of the PrepaCyte-CB kit)

The --------(b)(4)-------- freezing bag (510(k) cleared, ---(b)(4)---) is made from a special
----
----------(b)(4)----------

----------.

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

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

----------.

Reviewer Comment: *The bags used for collection, processing, and storing the HPC, Cord Blood are acceptable.*

COMPUTER SYSTEM

Donor eligibility information, lot release data, and HLA types are entered into (b)(4) and then transferred to the NMDP database to allow for cord blood bank searches. When a unit is requested for transplant, the original paper data is used to verify information. The paper batch records are stored in filing cabinets. They represent the primary source of data related to each unit and contain lot release results, donor eligibility data, storage location, and tracking of HPC, Cord Blood distribution.

Access to SLCBB HPC, Cord Blood Inventory, Search Procedure

Transplant centers can submit Search Registration Forms directly to the SLCBB or they can search SLCBB online for suitable units through the National Marrow Donor Program (NMDP) or by fax through the Caitlin Raymond International Registry (CRIR). (SE.03.09). In order for a transplant center to search and acquire units from the SLCBB, they must have experience with unrelated donor transplantation.

The St. Louis CBB uses -----(b)(4)----- program to store cord blood product data and identify potential matches based on search algorithm developed by SLCBB (SE.01.08). After the request for confirmatory testing is received, the unit is considered reserved for a period of ---(b)(4)---, the unit status is changed in ------(b)(4)------- to “reserved”, and the

confirmatory typing process is initiated. If the reservation expires, the transplant center is contacted to determine if they wish to continue to reserve the product or release it.

CONTROL OF ASEPTIC MANIPULATIONS

Control measures which minimize contamination of the CBUs are contained in SOPs for the various processes.

Aseptic Processing Validation

The validation of aseptic processing is not adequate, for the reasons stated in the 483 inspection comments:

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include adequate validation of the aseptic process. Specifically,

a. *Media growth promotion studies were not performed during the aseptic processing validation (media fill) of HPC-C processing; and*
b. *The media fill did not accurately reflect the actual manufacturing process since --(b)(4)-- was processed for the media fill and up to (b)(4) units can be processed simultaneously during actual production.*

These issues will need to be addressed prior to licensure, and should be addressed in the applicant's response to the 483.

ENVIRONMENTAL ASSESSMENT

Categorical exclusion per 21 CFR 25.31 (c) will be addressed by DMPQ.

LOT RELEASE TESTING

Criteria for Processing Cord Blood Units

The collected cord blood is evaluated at the manufacturing site prior to processing. In order for the cord blood to be processed it has to meet the criteria in Table 10.

TABLE 10. Acceptance criteria for cord blood processing

Parameter	Criterion
Inspection for bag integrity and clots	Bag must be intact and no clots present
Verification of donor identity	Maternal specimens and collection paperwork available
Total Nucleated Cell (TNC) count	TNC ---(b)(4)---
Cord blood volume	Cord blood volume (b)(4)

Listed below in Table 11 is a summary of the lot release tests that are performed on each unit of HPC, Cord Blood, the acceptance criteria, and test methods used. Infectious disease testing is performed on a maternal blood sample, HLA typing, and ABO/Rh typing are done using pre-processing cord blood samples, hemoglobin analysis is done using a sample from the red blood cell rich precipitate, sterility testing is done on the final by-product (FBP), and the rest of the testing is done on post-processing HPC, Cord Blood samples.

TABLE 11. SLCBB Lot release acceptance criteria

Product Characteristics	**Testing/Inspecting**	**HPC, Cord Blood (pre-cryopreservation) acceptance criteria**	**Test Method**
Safety	Infectious disease - 21CFR 1271.45 thru 1271.90	On maternal blood sample within 7 days of birth. 21CFR1271.80(a)(b) All tests negative except CMV, results are recorded	Performed using FDA licensed or approved test kits. Refer to TABLE 13 for details.
	Sterility – Bacterial/fungal cultures	No growth	----------(b)(4)----------
	Hemoglobin	No homozygous hemoglobinopathy	----------(b)(4)----------
Purity and Potency	Total nucleated cells (TNC)	$\geq 5.0 \times 10^8$ TNC/unit	Calculated using the -----(b)(4)-----
	Viability nucleated cells	≥ 85%	------(b)(4)------
	Viable CD34+ cell count	$\geq 1.25 \times 10^6$ / unit	Determined by ----------(b)(4)-------
	Colony Forming Units (CFU)	----------(b)(4)----------	----------(b)(4)----------
Identity	HLA typing (Confirmatory HLA typing Required*) Maternal HLA	HLA-A, B, C Antigens – ----------(b)(4)--------- HLA-DRB1, HLA-DQB1 Antigens – ----------(b)(4)---------- Haplotype match	----------(b)(4)----------
	ABO and Rh	Must match pre and post processing	---------- (b)(4)---------- ----------(b)(4)----------

*Prior to release for transplantation

SAFETY TESTING

1. Donor Eligibility

The donor eligibility (DE) procedures include screening and testing of the cord blood donors for risks of relevant communicable diseases or disease agents (RCDAD). In the initial pre-screening prior to the collection of collect blood, birth mothers are assessed for the following risk factors which are the initial exclusion criteria:

- Known positive serology for HIV, Hepatitis B or C, HTLV I/II, syphilis, gonorrhea
- Active sexually transmitted disease at the time of delivery
- Maternal high risk behavior (IV drug use, taking money or drugs for sex, etc.)
- Blood transfusion during labor and delivery
- Maternal and infant temperature greater than 102^{o}C F or 39^{o}C

If the above findings are discovered by the cord blood bank after collection, the cord blood unit is either discarded or used for research.

A) Donor Screening

Donor screening process includes the review of the donor's relevant medical records for clinical and physical examination records and the maternal risk questionnaires to identify risks for RCDADs. The clinical evidence and physical examination findings are documented on the Labor & Delivery form. The maternal medical and family history questionnaires are completed by the birth mother and sent to the cord blood bank along with the collected unit. If the collected unit is processed, the birth mother is contacted by a cord blood bank nurse within 2 weeks after the delivery to discuss and verify the information on the medical history questionnaire and to obtain additional information for any complications, infections or potential exposure of the mother and the baby to an infectious virus during or in the immediate post-partum period. The follow-up discussion with the birth mother is documented on the Medical History Questionnaire Review. If the maternal risk questionnaire was completed > 6 months prior to the cord blood collection, the entire questionnaire is reviewed with the birth mother and documented. In addition to the evaluation for RCDADs, the obstetrical nurses, physicians, or midwives also document additional information (e.g. meconium staining, maternal colonization with group B streptococcus, prolonged ruptured membrane, elevated maternal/infant temperature and antibiotic administration) on the Labor & Delivery form that do not impact the DE determination but the information is disclosed to the transplant centers.

Donors are screened for the following risk factors:

HIV 1/2, HTLV I/II, HBV, HCV, Syphilis, ----------(b)(4)----------, TSE (CJD/vCJD), Xenotransplantation

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

The SLCI uses the same donor screening procedures. However, the donor medical and family history questionnaires and the Labor & Delivery forms have the SLCI header.

Reviewer Comments:
In the initial submission, the donor screening SOPs did not define the process for review of the relevant medical records for clinical evidence of RCDADs in accordance with the 1271.75 regulations. The following draft SOP and forms were submitted on 6/26/12 (SN10) and the following needs to be addressed:

- *The draft SOP (CL.03.07) does not clarify that the findings disclosed to the transplant centers (e.g. antibiotic administration) will only be acceptable in absence of any infection. A CR letter comment related to this issue has been included.*
- *The finalized Labor and Delivery form used at the SLCBB and SLCI facility need to be submitted. Suggest including this comment in the AI letter.*

B) Donor Testing

The infectious disease tests are performed at contract testing laboratories:

TABLE 12. Contract Donor Testing Laboratories

Facility	Testing Laboratory	FDA Registration	CLIA Certification
SLCBB	----------(b)(4)----------	-----(b)(4)-----	-----(b)(4)-----
SLCI	----------(b)(4)----------	-----(b)(4)-----	-----(b)(4)-----

The testing laboratories are audited by the applicant to ensure compliance with FDA's donor testing requirements. Both testing laboratories are accredited by AABB and they participate in the proficiency testing program provided by the College of American Pathologists.

Maternal blood specimens for donor testing are obtained on the day of or within 7 days of the infant's birth. Birth mothers who receive blood transfusion during labor and delivery are excluded from donation. To determine the possibility of plasma dilution, on the Labor and Delivery form, the collection staff document whether or not the birth mothers have received >2000ml of IV fluid 1 hour prior to obtaining the donor testing specimen.

Reviewer comments:
In the original submission, there was no information regarding the assessment of birth mothers for the possibility of plasma dilution. The applicant added the documentation regarding the plasma dilution to the following draft documents which were submitted on 6/26/12 (SN10):

- *Labor and Delivery form used at SLCBB and the Saint Louis Cord Blood Bank Nursing Instructions for Cord Blood Collections Using the (b)(4) Sterile Cord Blood Collection Unit for Vaginal and Cesarean Deliveries form. The applicant needs to submit the finalized forms used at the SLCBB and SLCI facilities. Suggest including this comment in the AI letter.*

- *The draft SOP CL.06.08 includes instructions for documentation of plasma dilution but it does not define whether donors receiving >2000ml of IV fluids are considered eligible or ineligible. A CR letter comment related to this issue has been included .*

  In an email received on 7/20/12, the applicant state that donors who receive >2000ml of IV at the time of delivery will be rejected; however, the final SOP has not been submitted.

The blood collection tubes are labeled with hospital generated maternal labels (includes birth mother's name, medical record #, and the date of birth) by the collection staff and sent to the cord blood bank. Upon receipt by the processing laboratory, the donor identification is verified, a unique identification barcode label is assigned to the specimens, and the hospital label that includes the birth mother's information is removed. Maternal specimens are sent to the testing laboratory by the courier under contract with the cord blood bank. The specimens are shipped in validated shipping boxes following the testing laboratory's instructions (SLCBB SOP TS.010).

Note: Refer to the reviewer comment in the Donor Tracking section regarding the unique donor identification.

Reviewer comment: *The applicant needs to submit the specimen shipping information for the SLCI facility. A CR letter comment has been included.*

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

TABLE 13. Donor Infectious Disease Tests

Test	Test Kit Manufacturer	
	Performed by ---(b)(4)--- (SLCBB facility)	**Performed by (b)(4) (SLCI facility)**
(b)(4)HB(b)(4)	(b)(4)	(b)(4)
HB(b)(4)	(b)(4)	(b)(4)
(b)(4)HCV	(b)(4)	(b)(4)

Test	Test Kit Manufacturer	
	Performed by ---(b)(4)--- (SLCBB facility)	**Performed by (b)(4) (SLCI facility)**
(b)(4) HIV 1 and 2	(b)(4)	(b)(4)
(b)(4) HTLV I and II	(b)(4)	(b)(4)
(b)(4) HIV/HCV/HBV	(b)(4)	(b)(4)
Treponema pallidum	(b)(4)	(b)(4)
(b)(4)CMV	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)

HPC, Cord Blood units that are collected from birth mothers who test positive for the above tests are not banked for clinical use except for (b)(4)CMV and (b)(4)HB(b)(4). CMV results are reported to the transplant center but the results are not factored into the donor eligibility determination. If the (b)(4)HB(b)(4) result is positive but (b)(4)HBV is negative, the donor is considered ineligible (see Final Donor Eligibility Determination section). When a cord unit is selected for transplantation, at the time of confirmatory testing, a CMV (b)(4) is performed on a frozen sample from the HPC, Cord Blood unit if the maternal CMV -(b)(4)- result is positive.

Reviewer comments:

- *In the submission received on 6/26/12 (SN10), the applicant addressed a few discrepancies in SOPs related to syphilis and CMV testing (draft SOP TE04.03). The applicant needs to submit the final SLCBB SOP as well as SOPs used by the SLCI facility (SLCI-CTS 4031.01 and SLCI-CTS 4030.01). A CR letter comment related to this issue has been included.*
- *Several SOPs in the original submission referred to confirmatory and supplemental tests. In the letter received on 6/26/12 (SN10), the applicant confirmed that these tests are performed for donor notification purposes and are not factored in to the DE determination. This is acceptable.*
- *When a unit is selected for transplant, if the birth mother had tested positive for (b)(4) CMV, the applicant performs CMV (b)(4) on a (b)(4) sample of the cord unit. If the CMV (b)(4) is negative, the unit is made available for transplant. In the letter received on 6/26/12 (SN10), the applicant explained that the CMV (b)(4) performed on the (b)(4) sample of the unit is a research assay and the result is added as a comment to the report that is sent to the transplant center. The additional (b)(4) test performed by the applicant is not a requirement for donor eligibility determination, but if the test is performed and the results are used as release criteria, the test needs to be validated. Test results may not be reported for research purposes. A CR letter comment related to this issue has been included.*
- *The draft Comprehensive Matched Cord Blood Report that was emailed on 7/20/12 states that the "CMV (b)(4) testing is intended for research purposes only". The statement related to research test is not acceptable. The applicant needs to revise the report and to clearly distinguish tests that were performed using FDA-licensed,*

approved or cleared donor screening tests. A CR letter comment related to this issue has been included.

C) Final Donor Eligibility Determination

The DE determination process consists of two major steps. At any time during this process, the donor may be rejected or if the cord blood unit was already collected, the unit will be discarded if the donor is deemed ineligible.

1. Assessment of the birth mother and baby by obstetrical nurses, physicians or midwives for:
    a. High risk behaviors and other risk factors including but not limited to sexually transmitted diseases or prenatal infectious disease test results.
    b. Any abnormal findings in the birth mother and baby during the labor and delivery (e.g. blood transfusion or complications during delivery) as well as any RCDAD risk factors found during the review of clinical and physical examination records.

    The information is documented on the Labor and Delivery Data form which includes a detailed list of RCDAD risk factors that must be included in the donor evaluation.

2. Review of the donor screening and test results and final donor eligibility determination by the cord blood bank staff:

    a. Review of the donor and family history questionnaires, donor screening and test results.
    b. Follow-up with the birth mother within 2 weeks after delivery to verify and/or clarify the information (e.g. post-delivery complications, infections).
    c. Documentation of the final donor eligibility determination by the Quality Specialist in consultation with the medical director before the unit is made available in the search system.

Donors are deemed eligible if the donor screening does not identify any risk factor for RCDADs 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 (Comprehensive Matched Cord Blood Report), that accompanies the unit at the time of distribution, includes the listing and interpretation of all the infectious disease tests and the final donor eligibility determination.

The applicant determines donors with the following risk factors to be ineligible but the units may be released for clinical use under IND with documented urgent medical need:
- Positive (b)(4)HB(b)(4) result if (b)(4)HBV is negative
- Since 1977, donors or their sexual partners who were born in, traveled to, or lived for longer than 1 year in certain African countries (country names listed on the donor history questionnaire).

Note: On February 1, 2010, the applicant started using HIV (b)(4) donor screening test that has been licensed by FDA and is specifically labeled as sensitive for detection of HIV -------(b)(4)-------.

- Travel history to malarial or TSE-affected countries (country names listed on the donor history questionnaire).

The DE determination procedure is similar at both facilities but there are separate SOPs (SLCBB: TE.04.03; SLCI: SLCI-CTS 4030.01 and SLCI-CTS-4031.01). For units collected at the SLCI facility, the laboratory director performs the donor eligibility determination but the final DE and acceptance of the HPC, Cord Blood unit for transfer to the SLCBB facility is conducted by the Quality Specialist at the SLCBB facility after review of all the donor screening and testing documentation.

Reviewer Comments:

- *The donor eligibility SOPs submitted originally did not clearly define the criteria for eligible versus ineligible donors (SOPs referred to terminology such as "exception"). The applicant submitted draft SLCBB SOPs on 6/26/12 (SN10) which addressed most of the identified issues (CL13.10, TE.04.03, CL.03.07, Product Documentation/Tech Review Form) but the following discrepancies and clarifications need to be addressed:*

    - *In the draft SOP CL.03.07 (page 3, step e), please clarify whether donors with the listed findings are considered "eligible" or "ineligible" for DE determination purposes. Also, the applicant discloses to the transplant center, if the mother/infant has elevated temperature or received antibiotics during labor. The applicant should clarify that the conditions are acceptable only in absence of any suspicion related to infection.*
    - *The draft Product Documentation/Tech Review form submitted on 6/25/12 does not include an option for HPC, Cord Blood units collected from donors for whom DE was not completed and does not identify whether an HPC, Cord Blood unit categorized as "available", is acceptable for licensure or release under IND.*

  The applicant needs to address the issues and submit the finalized SOPs including those used by the SLCI facility (SLCI-CTS 4031 and Product Documentation/Tech Review Form). A CR letter comment related to this issue has been included.

  The following two points should be communicated as AI comments:
    - *According to the donor questionnaires and draft SOP TE04.03, donors with history of travel to certain risk areas are accepted but donors are determined ineligible and units are used under IND; however, according to the draft SOP CL.13.10 (step 3), units from ineligible donors are discarded or used for research.*

- *According to SOP TE.04.03 (step 5), donors with positive HB(b)(4) or travel history to certain risk areas are ineligible and units are made available for transplant under IND. However, the Procedure Note section states that the products from ineligible donors are discarded or retained for research use.*

2. Sterility Testing

A) Sterility test procedure and lot-release specification

The applicant of BLA 125413, Saint Louis Cord Blood Bank (SLCBB) has two sterility testing facilities:

a. The SLCBB in-house facility for testing the HPC, Cord Blood units manufactured in Saint Louis and
b. The Saint Luke's Cancer Institute (SLCI) in-house facility for testing the HPC, Cord Blood units manufactured in Kansas City.

For sterility testing the SLCBB in-house facility will use ----------(b)(4)---------- culture bottles. The SLCI in-house facility will use the same media battery but a different model of detection system, the ---------(b)(4)----------. Both facilities will follow the same standard operating procedure (SOP) for the test, test each lot of HPC, Cord Blood and use the ---------(b)(4)--------- processed from each cord blood unit as the test sample. The product release specification (ref: Table 1 of STN: BL 125413/0, modified November 29, 2011) is no growth in all (b)(4) types of culture bottles.

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

Information on the working principle of the ---(b)(4)--- systems and compositions of the media bottles are available from ---(b)(4)---.

The ---(b)(4)--- detection systems and culture bottles are 510(k) cleared by FDA for diagnostic uses and testing of platelets.

SOP for the sterility test:

The sponsor has submitted a draft SOP (MI.02.01) for the sterility test, and has indicated that the SOP will be updated when the validation studies for the SLCI site are complete.

Reviewer Notes:

1. *The submitted SOP (MI.02.01) for the sterility test is not specific for testing HPC, Cord Blood products.*
2. *The SOP does not comply with 21 CFR § 610.12 (c)(1)(i)(A) and 21 CFR § 610.12 (c)(1)(i)(C) due to the following reasons:*

- *The anaerobic medium indicated in the SOP is different from the one used during assay validation,*
- *Neither the SOP nor the assay validation protocol specify an incubation temperature, and*
- *The proposed incubation time is -(b)(4)-, is not adequately supported by assay validation data, as discussed below.*

3. *Regarding qualification of each lot of culture media, the SOPP suggests but does not clearly state that lots of fungal bottles may be tested and aerobic and anaerobic bottles may be accepted based on manufacturer's COA.*

Letter comments addressing all the above issues are recommended.

B) **Sample used for the sterility test**

To preserve the majority of the HPC Cord Blood for transplant, the proposed sterility test will use the ----------(b)(4)---------- as -(b)(4)- sample - ---(b)(4)--- each for the aerobic and anaerobic media and (b)(4) for the fungal media.

The (b)(4) is prepared as follows:

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

The sponsor has provided approximate compositions of the ---(b)(4)--- HPC, Cord Blood unit (Table 14).

(b)(4)

Reviewer Notes:

1. *The applicant originally stated that a (b)(4) sample of the (b)(4) product would be tested in aerobic bottles, however they subsequently decided not to perform testing and communicated this in a tcon (ref: telephone conversation May 16th, 2012). The SOPP should be revised accordingly, this will be communicated in an AI comment.*
2. *The use of the (b)(4) as -(b)(4)- sample seems reasonable due to the following reasons:*

    a) *The sponsor has conducted a study to demonstrate that the proposed volumes of the (b)(4) test sample ---(b)(4)--- are adequate to capture low levels of bioburden. For these studies sterile whole cord blood units mixed with CPD anti-coagulant and PrepaCyte-CB reagent were intentionally contaminated to a final concentration of ---(b)(4)--- of test microorganisms. The units were then processed following the standard protocol to separate the (b)(4) cord blood fractions and the fractions inoculated into appropriate culture bottles to detect the contamination. The data (Table 15) suggest that ----------(b)(4)---------- are adequate and in some cases better than using --------(b)(4)--------- cord blood to capture that low level contamination.*

TABLE 15. A contamination of ---(b)(4)--- could be captured in the proposed volumes of the ------(b)(4)------

(b)(4)

(b)(4)

    b) *As the CBU fraction volume is ~25 ml (without DMSO and dextran) and it will be stored in a single container, testing ----------(b)(4)---------- of --(b)(4)--- sample for the sterility test is reasonable – complies with 21 CFR § 610.12 (d)(1) and 21 CFR § 610.12 (d)(3).*

    c) *The --(b)(4)-- the final product are derived from the same process and at the same time – complies with 21 CFR § 610.12 (d)(2).*

d) *The test sample volumes proposed for the sterility test are identical to the maximum volumes recommended by -----(b)(4)---- – complies with 21 CFR § 610.12 (d)(5).*

e) *The sponsor has indicated that they would not exclude mothers on perinatal prophylactic antibiotic as cord blood donors (ref: telephone conversation May 16th, 2012). As antibiotics would cross the placenta (ref: Ginsburg J, Annu. Rev. Pharmacol. 1971.11:387-408), the (b)(4) derived from the cord blood units isolated from these mothers could inhibit the sterility test and give false negative results. However, as the proposed aerobic and anaerobic media contain adequate quantities of ----------(b)(4)---------- capable of neutralizing:*

- *a very broad range of antibiotics and*
- *antibiotics present in the test sample at physiologically relevant concentrations (ref: BL 125413\0\8 - document/publication from ----------(b)(4)----------, the sponsor is in compliance with 21 CFR § 610.12 (c)(4) and § 610.12 (d)(4).*

C) Sterility Assay Validation

Assay validation data submitted to date are all related to the SLCBB in-house facility. The assay validation was done in ----------(b)(4)---------- of the study (ref: submission serial # 006) verified the following parameters:

a. Qualification of the ----------(b)(4)---------- – done by technician from (b)(4) and the result was satisfactory.
b. Growth promotion quality of the ---(b)(4)--- media – done by checking the growth of a limited number of test microorganisms in ---(b)(4)--- different lots of ---(b)(4)--- media and using ----(b)(4)---- CFU / bottle inoculum.
c. Assessment of the risk of getting false positive results from the test sample components – the test found that none of the test sample components flagged a positive result after 14 days of incubation.
d. Adequacy of the used test sample volume to capture low levels of contamination – for comments please see 'Sample used for the sterility test' above.

The (b)(4) of the study (ref: submission serial # 006) verified assay specificity, sensitivity, reproducibility, and Bacteriostatic/Fungistatic properties of the proposed test sample. The validation plan was executed by inoculating each of the -----(b)(4)------ (as shown in Table 16) with appropriate volumes of (b)(4) sample and ---(b)(4)--- CFU of test microorganisms and then comparing their minimum detection times to the saline controls. All test (b)(4) for the ----(b)(4)---- studies were incubated until flagged positive or for at least 14 days.

TABLE 16. Sterility Assay Validation Data show no significant Bacteriostasis / Fungistasis from the (b)(4) sample

(b)(4)

(b)(4)

Reviewer Notes:

1. *The panel of test microorganisms (to test assay specificity) and the -----(b)(4)----- CFU / bottle inoculum level (to test limit of detection) used for the validation of the growth promotion and bacteriostasis/fungistasis tests are acceptable.*

2. *The growth promotion assay was done in --(b)(4)-- and as growths could be detected within (b)(4) for bacteria (except the slow growing -(b)(4)-; ref: serial # 006 and BL 125413\0\8) and (b)(4) for fungi (ref: (b)(4) data from submission 006) the assay is reproducible and acceptable - complies with 21 CFR § 610.12 (c)(1)(i)(B) and 21 CFR § 610.12 (e)(1).*

3. *The validation study (for the SLCBB in-house facility only) has demonstrated that the proposed ---(b)(4)--- sample, (b)(4), does not have a bacteriostatic/fungistatic effect – complies with 21 CFR § 610.12 (b)(1). These studies were done in ---(b)(4)--- and the minimum detection times in the presence of the ---(b)(4)--- sample are consistent for all test microorganisms – complies with 21 CFR § 610.12 (b)(2) and 21 CFR § 610.12 (b)(3).*

   ***Note:** The data from the Kansas City in-house facility are pending and therefore the overall assay validation is incomplete.*

4. *The sponsor has provided data (ref: BL 125413\0\8) to show assay ruggedness and robustness. In these experiments the detection times were compared by growing the test microorganisms: i) in ----(b)(4)---- lots of media and ii) using a -----(b)(4)------ time to loading by keeping the cultures at --------(b)(4)--------. Comparable detection times and growth curves suggest that the assay has reasonable ruggedness and robustness.*

5. *There will be no repeat test for the sterility assay under any circumstances – therefore 21 CFR § 610.12 (f) is not applicable.*

6. *Due to inherent limitation of the sampling method used for the sterility test (especially under low bioburden conditions) and the fact that the processed cord blood final product is not suitable for terminal sterilization, the HPC, Cord Blood product should not be labeled as sterile.*

Incubation time

The applicant's default incubation time is (b)(4) (ref: SOP MI.02.01). To assess the adequacy of this incubation period all raw validation data (ref: Attachment B from submission serial number 06) were considered in addition to the data presented in Table 16.

Reviewer Notes:

We found that when a ----(b)(4)---- CFU / bottle inoculum was used for the (b)(4) slow growing microorganisms (----------(b)(4)----------) the consistency of the minimum time to detection was significantly reduced. For example, for the (b)(4) CFU / bottle inoculum of -------(b)(4)---------, one of the replicates did not grow and the time to detection for another replicate was --------(b)(4)---------- (data from SN06, not included in the Table 16). Additionally, no studies were done using stressed microorganisms – they might take longer to grow to a detectable level and that could significantly increase their minimum time to detection. In consideration of these points and the fact that validation data from SLCI have not been submitted, we recommend that the sponsor

incubate all of their sterility test samples for the licensed product for 14 days instead of ----(b)(4)---.

Overall Reviewer Assessment for the Sterility Test

Based on the information submitted through SN11 (received 6/26/2011), the proposed sterility test method and release specifications for BLA 125413 are not acceptable at this time due to incomplete assay validation [deficient to comply with 21 CFR § 610.12 (b)(2)] and deficiency in the written standard operating procedure [deficient to comply with 21 CFR § 610.12 (c)(1)(i)(C)].

The following outstanding issues on the sterility test should be communicated to the applicant in a CR letter:

1. *The validation studies done for the Saint Louis in-house sterility testing facility have demonstrated that the ----------(b)(4)---------- culture ----(b)(4)---- are suitable to grow/detect a wide variety of microorganisms. However, as the validation data are pending from the Kansas City in-house testing facility the overall assay validation is incomplete.*
2. *The SOP for the sterility test needs to be updated showing adequately validated incubation time and temperature, and the ---(b)(4)--- culture -(b)(4)- that will be used, and how qualification of each lot of ---(b)(4)-- culture media will be performed.*
3. *Based on the submitted validation data an incubation time of 14 days would be acceptable.*

An AI comment should be sent to the applicant to request documentation to the BLA that the (b)(4) of the (b)(4) product will not be included in the sterility test.

3. Hemoglobin Testing for Homozygous Hemoglobinopathy

Both SLCBB and SLCI use the contract testing lab, ----------(b)(4)----------, to perform hemoglobinopathy testing on cord blood samples. The first line of testing performed is ----------(b)(4)----------. The normal cord blood pattern is ----------(b)(4)----------

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Hemoglobin - Method Validation/Verification

SLCBB provided vendor qualification criteria (SOP QM.05D.03) for the contract testing lab, ----------(b)(4)---------- who performs Hemoglobin electrophoresis analysis of CBUs. --(b)(4)-- is CLIA certified (CLIA ID # ----(b)(4)----). SLCBB provided --(b)(4)-- biannual 2010 and 2011 Hemoglobinopathy proficiency testing surveys administered by the College of American Pathologists (CAP), reporting no significant discrepancies during this period. SLCBB also provided --(b)(4)-- hemoglobin protein chemistry method validation data performed for ------(b)(4)------ methods: ----------(b)(4)---------- as compared to (b)(4) for reference. Here, (b)(4) samples previously diagnosed with a hemoglobin disorder by (b)(4) were randomly chosen from (b)(4) clinical patient population. These hemoglobinopathies represented different patterns (e.g. heterozygous, homozygous, traits, Hb Bart's, etc). All (b)(4) whole blood samples were collected in ----------(b)(4)---------- was used for the validation tests. (b)(4) reported the (b)(4) methods tested (performed in (b)(4)) produced the same hemoglobin phenotype/pattern results as (b)(4) for all (b)(4) samples. (b)(4) reported similar results for SLCBB's CBU samples. (b)(4) states method SOPs are in place and approved by the Hemoglobin Reference Laboratory director.

Review Comment: *The validation information appears to be adequate to support the applicant's use of (b)(4) as a contract testing lab for hemoglobinopathy testing.*

PURITY & POTENCY:

1. Total Nucleated Cells (TNC)

The --------(b)(4)-------- is an FDA-cleared (510(k) number ----------(b)(4)---------- for analysis of many hematological parameters including ----------(b)(4)----------. The applicant defines TNC as ---------(b)(4)--------- with a release limit of TNC (b)(4) (SOP TE04.01). The applicant acknowledges the ------(b)(4)------ is FDA-cleared, states use of the instrument according to the manufacturer's instructions and submitted verification of results in their facility (see Tables 18 and 19).

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

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TABLE 17. ---(b)(4)--- Reagents for TNC Testing

(b)(4)

(b)(4)

Total Nucleated Cells (TNC) - Method Validation/Verification

A) SLCBB: TNC Count (-------(b)(4)-------)

SLCBB has documentation for their ----------(b)(4)---------- installation and calibration by -(b)(4)- service and technical representatives, and operational performance qualification. SLCBB performs preventive maintenance, system calibration, and quality control testing/analysis. Routine daily maintenance is performed including a daily system self check of background counts expected to be within acceptable limits (------(b)(4)------ for WBC count). SLCBB submitted a 1-month sample of their daily preventative maintenance. SLCBB submitted a sample of daily QC results (Levey-Jennings control charts) and indicates that QC analysis and CBU testing results are evaluated daily to monitor consistency of equipment performance. Additionally, SLCBB participates in the ----------(b)(4)---------- Quality Assurance Program (QAP) comparing their QC analysis with peer group results. SLCBB participates in periodic proficiency testing of system performance and method precision through 2 independent College of American Pathologists (CAP) hematology surveys: one for CBC/Diff counts and one for calibration verification/assay linearity of WBC and nRBC count. SLCBB performed in-house hematology analysis of different CBU product samples (pre-processing, post-processing, and buffy coat).

Review Comment: *The ---(b)(4)--- SOPs (TS.09.08 and SLHS "Procedure: -----(b)(4)----------") indicate the use of the commercially available stabilized human blood QC control product, ----------(b)(4)----------; however, the documents also refer to this as "----------(b)(4)----". The applicant should revise their SOPs for consistency in referring to the QC control material as "-----(b)(4)-----". An AI letter comment will be submitted to address this issue.*

Summary of SLCBB Validation Studies:
The applicant did not conduct validation with a traditional pre-defined validation plan, but their assays function appropriately with demonstration of assay performance. SLCBB provided ------(b)(4)------ data including accuracy, precision, linearity, and orthogonal

2 pages redacted (b)(4)

(b)(4)

Review Comment: *The validation information appears to be adequate to support SLCBB's use of ----(b)(4)---- to evaluate -------(b)(4)------ for TNC analysis.*

B) SLCI: TNC Count (--------(b)(4)---------)

SLCI has an agreement with Saint Luke's Regional Laboratory (SLRL)/Hematology Section to use their ----------(b)(4)---------- for TNC testing. SLCI/SLRL provided documentation for -------(b)(4)------- installation and calibration by --(b)(4)- service and technical representatives, and operational performance qualification. SLRL performs preventive maintenance, system calibration and quality control testing/analysis. SLCI/SLRL provided samples of their daily preventative maintenance. SLCI/SLRL provided samples of daily QC results (Levey-Jennings control charts) and indicates that QC analysis and CBU testing results are evaluated daily. Additionally, SLRL participates in the ----------(b)(4)---------- Quality Assurance Program (QAP) comparing their QC analysis with peer group results. SLRL participates in periodic proficiency testing of system performance and method precision through 2 independent CAP hematology surveys: one for CBC/Diff counts and one for calibration verification/assay linearity of WBC and nRBC count.

- Summary of SLCI Validation Studies:

SLCI's validation submission was not complete as of this review. SLCI did provide some data on the 'primary' ----------(b)(4)---------- but not for the ----------(b)(4)----------. SLCI provided -------(b)(4)------- data intended to show accuracy, precision, linearity (Table 19); however, clarification is needed regarding the sample types and acceptance criteria. Two CR letter comments were included to address these issues (see comments 23 and 24). Additional discussion follows Table 19.

TABLE 19: Validation Summary for SLCI TNC

(b)(4)

(b)(4)

Unresolved SLCI Issues: (Re: my 5/10/12 comments to the applicant):

• Please submit validation data comparing the ----------(b)(4)-------- instruments currently in use (--------(b)(4)---------) including analysis of cord blood samples for relevant parameters (e.g. -----(b)(4)-----).

• Regarding your SN02 submission (Req 4b: 2/4) that included cell count "linearity data" for the SLCI ----------(b)(4)----------, please clarify the types of samples tested and clarify your acceptance criteria.

No response received from the applicant as of this review.

***Reviewer comment**: Inadequate information was submitted to evaluate SLCI's use of -------(b)(4)-------- to enumerate WBCs and nRBCs for TNC analysis in cord blood samples. Two CR letter comments are included to address this issue.*

2. Viable Nucleated Cells

Description: Both SLCBB and SLCI use the same ----------(b)(4)---------- procedure as the primary measure of cell viability (SOP TS.04.05). CBU samples are
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---(b)(4)----------.

***Review comment**: During the SLCBB inspection it was observed that a ----------(b)(4)- was not used by the technician to keep track of the viable and non-viable cell count. This was discussed with the applicant who will update SLCBB SOP TS.04.05 and SLCI SOP TS.04 to include use of a -------(b)(4)------- and a description of their use of the ---------(b)(4)----------. This was previously communicated to the applicant as an item on the Inspectional Observations Form 483 regarding SOPs lacking sufficient detail to ensure consistent performance.*

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

Viable Nucleated Cells - Method Validation/Verification

SLCBB submitted viability data on post-processing and pre-cryopreservation CBU samples intended for method comparison of ----------(b)(4)---------

1 page redacted (b)(4)

(b)(4)

Additionally, SLCBB and SLCI perform internal semi-annual proficiency testing (e.g. SOP SLCI-CTS 101.01) of cell processing laboratory personnel for the ---(b)(4)--- viability method with intra-comparison among individual results (------(b)(4)------) and inter-comparison with an ----------(b)(4)---------- determination (-----(b)(4)----) as reference.

Unresolved SLCI Issue: (Re: my 5/10/12 comments to the applicant):

• In the 11/29/2011 submission, Appendix U was submitted containing viability data of SLCBB processed cord blood intended for method comparison of ----------(b)(4)----------. Please clarify if this method comparison was performed at SLCI.

No response received from the applicant as of this review.

***Review comment**: The validation information appears to be adequate to support SLCBB's use of ---(b)(4)--- as a primary method for viability testing; however, sufficient documentation for SLCI was not submitted. Additional documentation for SLCI was requested on 5/11/12 but was not received as of this review. SLCI should also submit method comparison of cord blood viability using ----------(b)(4)---------- and an evaluation of viability sample stability. A CR letter comment is included to address this issue.*

3. Viable CD34 counts

Description: CD34+ hematopoietic progenitor cells are measured by -----(b)(4)------ including ---(b)(4)--- with commercially available -----(b)(4)----- antibody kits for CD34, ------(b)(4)----- viability. ----------(b)(4)----------. CBU aliquots are tested ----------(b)(4)---------- as per SOPs (SLCBB's TS.03.06 and SLCI/SLRL's "CD34 Stem Cell Quantitation"). The applicant's release limit per CBU is CD34+ cells $\geq 1.25 \times 10^6$.

A) Instruments, Reagents and Methods - Overview

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

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

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(b)(4)

1 page redacted (b)(4)

(b)(4)

B) SLCBB CD34+ Cell Viability - -------(b)(4)------ Equipment

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

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

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

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

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

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

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C) SLCBB CD34+ Cell viability - Method Validation/Verification

Validation Plan for CD34/(b)(4) cell count and viability –The approach taken to implement of the -(b)(4)- protocol included:

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

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TABLE 21: SLCBB's CD34 Validation Plan and Results

(b)(4)

1 page redacted (b)(4)

(b)(4)

Overall Reviewer Assessment for SLCBB ------(b)(4)-------

SLCBB adequately validated their --------(b)(4)------- procedures. SOPs, instrument qualification, reagent qualification, and quality controls of the assay appear to be adequate to ensure consistent performance of this assay as part of manufacturing. Adequate procedures for instrument quality control, instrument validation, installation of new -------(b)(4)-------, and training of staff appear to be in place.

D) SLCI CD34+ Cell Viability - ------(b)(4)------- Equipment

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

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

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

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E) SLCI CD34+ Cell viability - Method Validation/Verification

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

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(b)(4)

(b)(4)

Unresolved SLCI Issues: (Re: my 5/10/12 comments to the applicant):

The SN03 submission (Req 4b, 3/4, submitted 12/13/11) included an SLCI report titled "New Instrument Validation ----------(b)(4)----------.

- Please provide additional description on the type of samples analyzed throughout this report and clarify the acceptance criteria for all parameters.
- Please submit validation data for the ----------(b)(4)---------- that includes analysis of cord blood samples for relevant parameters (e.g. CD34/----(b)(4)----).

The SN03 submission (Req 4b, 4/4, submitted 12/13/11) included a cord blood (b)(4) comparison between SLCBB and SLCI.

• Please clarify your acceptance criteria used for this comparison.

No response received from the applicant as of this review.

***Review comment**: Inadequate information was submitted to evaluate SLCI's use of ----(b)(4)---- to enumerate viable CD34+ cells in cord blood samples. Validation information was only provided on (b)(4) instruments used for the CD34+ cell assay. Two CR letter comments are included to address this issue.*

The SN03 submission (Req 4b, 4/4, submitted 12/13/11) included a cord blood (b)(4) comparison between SLCBB and SLCI.

• While you indicated that the (b)(4) validation data between SLCBB and SLCI used the ----------(b)(4)---------- instrument, some data sets note --(b)(4)-- use. Please clarify and describe the analyzers used and provide unique identifiers (e.g. model/serial numbers such as ----------(b)(4)----------, etc.).

No response received from the applicant as of this review.

***Review comment**: This issue will be communicated as an AI comment.*

4. Colony-Forming Unit (CFU) Assay

Description: SLCBB states their colony-forming cell (CFC) or colony-forming unit (CFU) assay (SLCBB SOP TS.05.06; used by SLCI) allows functional and quantitative assessment of cord blood hematopoietic progenitors. When incubated in ----------(b)(4)----------, the hematopoietic stem cells present in cord blood are expected to multiply, producing colonies of specific cell lineages according to their level of maturity. This assay is intended to estimate/measure the frequency and proliferative/reconstitutive ability of hematopoietic stem cells in cell preparations used for transplantation, and the applicant considers it a surrogate measure of product functionality and potency.

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

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

Colony-Forming Unit (CFU) Assay - Method Validation/Verification

The applicant provided a correlation analysis comparing total CFU colonies counted from (b)(4) CBU samples by SLCBB vs. SLCI, resulting in a R^2 value of (b)(4). Additionally, individual colony components (----------(b)(4)----------) were analyzed and results appeared to be similar.

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

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

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

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Competency of technical staff for CFU assay and scoring of plates is done twice a year. SLCBB and SLCI subscribe to ----------(b)(4)---------- CAP's Stem Cell Processing proficiency testing programs with trained personnel participating at acceptable performance. Internal proficiency is monitored semi-annually. All trained technicians will score the same 3 assays and the coefficient variation of total colonies present should not exceed (b)(4). If a technician is outside of acceptable range the laboratory director will examine proficiency testing to decide if further training is needed.

Review Comment: *The applicant performed validation for the semi-quantitative CFU assay including optimization of culture conditions, internal and external proficiency testing and correlation analysis of CFU colonies enumerated by SLCBB and SLCI. The R^2 value of (b)(4) is (b)(4) for an assay susceptible to observer variability. The validation information appears to be adequate to support the applicant's CFU assay performance.*

IDENTITY

1. ABO Blood Group & Rh Type

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

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

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

(b)(4)

(b)(4)

ABO/Rh - Method Validation/Verification

SLCBB submitted validation data of their ABO blood typing method of umbilical CBUs (harvest in (b)(4) CPD anticoagulant) as compared to (b)(4) electronic health records ((b)(4) records) for cord blood donors that were born at SSM hospitals. All (b)(4) CBU typing results obtained by SLCBB were compared with the ABO blood type of the donor in the medical record and found to have the identical blood type. Similarly, SLCI submitted SLRL's Transfusion Service Lab validation data including audit reports of CBU blood typing as compared to (b)(4) workstation electronic health records of 4 participating Saint Luke's hospitals (SLH, SLS, SLE, SLN). All (b)(4) CBU typing results obtained by SLCI/SLRL were identical to the blood type results in the medical record.

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

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Review Comment: *The validation information appears to be adequate to support the use of SLCBB's - (b)(4)- ABO/Rh ------(b)(4)------ test and SLCI's use of the SLRL Blood Bank Department (---(b)(4)---) for ABO/Rh typing.*

2. HLA typing

Description: Both SLCBB and SLCI use a contract testing lab, ----------(b)(4)----------, for HLA typing of umbilical cord blood and maternal samples (recruitment, initial, confirmatory, verification or resolution). SLCBB submitted SOP TS.02.04 (applies to SLCI) for shipping samples to the outside contractor, ----(b)(4)---- Samples include ----------(b)(4)---------- that are shipped via ---(b)(4)--- courier.

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

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

HLA Typing - Method Validation/Verification

SLCBB provided their vendor qualification criteria (SOP QM.05D.03) for the contract testing lab, ----------(b)(4)----------, used for HLA typing of umbilical cord blood and maternal samples. ----------(b)(4)---------- is CLIA certified (CLIA ID # ----(b)(4)----) and accredited by the American Society for Histocompatibility and Immunogenetics (ASHI, # ---------(b)(4)---------- participates in the ASHI proficiency testing program for -----(b)(4)----- typing of Class I and Class II HLA loci. SLCBB provided --(b)(4)-- biannual 2011 HLA Class I (A, B, C) and Class II (DR, DQ, DP) molecular typing proficiency testing surveys administered by the College of American Pathologists (CAP), reporting no significant discrepancies during this period.

--(b)(4)-- reports their in-house developed SBT and SSOP procedures have been in routine use for their NMDP contracts and are subject to continuous assessment in their blind QC program as part of our typing contract. ---(b)(4)-- states this process continuously revalidates all new reagents (--------(b)(4)---------) as they are put into

routine use. --(b)(4)-- states that during -(b)(4)- of molecular typing for NMDP -(b)(4)- has never exceeded the error threshold as defined in the NMDP contracts.

Review Comment: *The validation information appears to be adequate to support the applicant's use of --(b)(4)-- as a contract testing lab for HLA testing.*