

**BLA 125764
CMC Review of Resubmission**

**REGENECYTE (HPC, Cord Blood)
StemCyte, Inc.
13800 Live Oak Ave, Baldwin Park, CA 91706, USA**

**Cell Therapy Branch 1 (CTB1)
Division of Cell Therapy 1 (DCT1)
Office of Cellular Therapy and Human Tissue CMC (OCTHT)
Office of Therapeutic Product (OTP)**

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1. BIOLOGICS LICENSE APPLICATION NUMBER

125764

2. APPLICANT NAME AND LICENSE NUMBER

StemCyte, Inc., 13800 Live Oak Ave, Baldwin Park, CA 91706, USA

License number: 2280

3. PRODUCT NAME/PRODUCT TYPE

Proprietary Name: REGENECYTE

Non-Proprietary Name: Hematopoietic Progenitor Cells, Cord Blood (HPC, Cord Blood)

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

The Drug Product (DP) is volume- and red blood cell-reduced allogeneic unrelated umbilical cord blood called the HPC, Cord Blood. The HPC, Cord Blood contains a minimum of 9×10^8 nucleated cells in a 25ml mixture of 10% Dimethyl sulfoxide (DMSO) and 1% Dextran 40. The HPC, Cord Blood is stored in a two-compartment cryobag and stored in vapor phase of liquid nitrogen ($\leq -150^\circ\text{C}$).

5. MAJOR MILESTONES

BLA Submission Date: January 7, 2022

First Committee Meeting: Feb. 3, 2022

Filing Meeting: February 28, 2022

60-day Filing Date: Mar. 8, 2022

Internal Mid-cycle Meeting: July 8, 2022

Internal Late-cycle Meeting: Nov. 7, 2022

Advisory Committee Meeting: N/A

BLA Review Data Cutoff Date: November 22, 2022

Action Due Date: January 6, 2023

Complete Response Letter Date: January 20, 2023

Resubmission Date: November 9, 2023

Kick-off Meeting: November 28, 2023

Mid-Cycle Status Meeting: February 12, 2024

Action Due Date: May 10, 2024

6. CMC/QUALITY REVIEW TEAM

Reviewer/ Affiliation	Submission Subject Reviewed
Fatima Abbasi, MS, MPH, CBER/OTP/OCTHT/DCT1/CTTB	Flow cytometry

Hanh Khuu, MD, CBER/OTP/OCTHT/DHT/HTRS	Donor testing and screening
Mercy Quagraine, PhD, CBER/OTP/OCTHT/DCT1/CTB1	Identity, viability, and stability testing
Saravanan Karumbayaram, M.Pharm., PhD (Chair), CBER/OTP/OCTHT/DCT1/CTB1	Rest of the CMC sections, including, but not limited to, CBU site qualification and collection, shipping, raw material, manufacturing, sterility assay, entire process validation, final product shipping, labeling, and tracking, environmental assessment, final CMC memo drafting and compiling

7. INTER-CENTER CONSULTS

None

8. SUBMISSIONS REVIEWED

Date Received	Submission	Comments/ Status
01/07/2022	125764/0.0	Original submission
04/08/2022	125764/0.3	Production Schedule for Inspection (D)
04/29/2022	125764/0.4	(b) (4) assay; (b) (4) viability; ABO/Rh testing; CAP Proficiency Test and HLA Test
05/03/2022	125764/0.5	Donor eligibility testing and screening; ISBT labeling system; UID barcodes; CBU collection and storage; TNC count; NRBC count; stability study; Dextran concentration in wash buffer
05/23/2022	125764/0.6	Draft Labeling
05/27/2022	125764/0.7	UID Bar Code – Executed batch record that is representative identification codes, sequences, donor screening for Zika; IDM testing contract site clarification.
06/07/2022	125764/0.8	Request for SOPs and documents-COC; donor eligibility; employee training; collection and delivery; cord blood disposition; QA batch release review; executed batch record; final product review and release

06/30/2022	125764/0.9	(b) (4) CD34 enumeration; flow cytometry validation for CD34, (b) (4) and viability
07/01/2022	125764/0.10	Sterility assay sample (b) (4) (b) (4) bacteriostasis/fungistasis or method suitability assay
07/27/2022	125764/0.13	Sterility assay – sampling; sample volume; method suitability report; sterility investigation;
07/29/2022	125764/0.14	Information about materials used – (b) (4) CPD Collection bags;
08/02/2022	125764/0.15	510(k) number for collection bags; integrity of collection bags; manufacturing process; qualification of the (b) (4) Medical Transporter; Load for dry shipper; Computer systems
08/24/2022	125764/0.18	Donor eligibility SOPs
09/08/2022	125764/0.19	Follow-up on donor eligibility SOPs
09/26/2022	125764/0.20	483 Response to CMC comments
09/29/2022	125764/0.22	CBU Transport; Sterility; computer systems
09/30/2022	125764/0.23	Sterility testing; sampling plan; sterility assay method suitability report
10/21/2022	125764/0.24	Donor eligibility testing – acceptance criteria; Process validation; CD34 enumeration; (b) (4) Preventive Maintenance
10/31/2022	125764/0.25	483 CMC Response-Hetastarch addition; shipping simulation; (b) (4) viability revalidation
10/31/2022	125764/0.26	(b) (4) shipper validation; (b) (4) (b) (4) addition for Hetastarch and cryoprotectant addition; computer system
10/31/2022	125764/0.27	(b) (4) viability validation; Stability studies expiry dating
11/14/2022	125764/0.28	Validation of cord blood processing using (b) (4) Computer systems
11/14/2022	125764/0.29	Growth promotion test; (b) (4) assay;
11/18/2022	125764/0.30	Flow cytometry validation
11/22/2022	125764/0.31	Flow cytometry validation; (b) (4) linearity; Sterility testing reading microbial growth; (b) (4) viability; (b) (4)

11/22/2022	125764/0.32	483 responses
Amendments Reviewed After Complete Response Letter		
12/21/2022	125764/0.33	Updated response to donor testing and screening, (b) (4) viability assay and flowcytometry. This amendment was received after the data cutoff date (11/22/2022) and not reviewed.
03/09/2023	125764/0.34	Request for Type A meeting to discuss deficiencies raised by the Agency on the Complete Response Letter. Meeting was denied as the questions can be addressed on an informal telecon meeting was held on May 9, 2023, and clarifications were provided.
11/09/2023	125764/0.35	Resubmission addressing Complete Response deficiencies
12/14/2023	125764/0.37	Applicant response to DHT IR dated November 30, 2023
02/09/2024	125764/0.38	Applicant response to CMC, DHT and DMPQ IRs
03/14/2024	125764/0.39	Applicant response to CMC IR
03/15/2024	125764/0.40	Request to be exempted from the barcode label requirements
04/02/2024	125764/0.41	Applicant response to PI, labeling and CMC IRs
04/05/2024	125764/0.42	Response to IRs for labeling dated April 2nd, 2024
04/10/2024	125764/0.43	Partial response to IR dated April 2, 2024
04/25/2024	125764/0.44	Response to IR dated April 22, 2024
08/16/2024	124764/0.45	Response to IR for proposed USPI edits dated August 7th, 2024
09/06/2024	125764/0.46	Response to IR for proposed USPI edits dated September 6th, 2024
09/16/2024	125764/0.47	Response to IR for proposed USPI edits dated September 13th, 2024
10/02/2024	125764/0.48	Applicant submitted an updated tie-tag label
10/18/2024	125764/0.49	Applicant submitted final draft USPI (United States Prescribing Information), PDF and MS Word version and final draft tie tag label

9. REFERENCED REGULATORY SUBMISSIONS

None

10. EXECUTIVE SUMMARY AND RECOMMENDATION

A. Executive Summary

The Applicant for this BLA is StemCyte (BLA STN 125764/0.0). The StemCyte manufacturing facility is in Baldwin Park, CA. The proprietary name for the product is REGENECYTE. Each lot of the product is manufactured from (b) (4) (b) (4) (b) (4) is minimally manipulated by reducing volume and red blood cells (RBCs), which is termed the red cell reduced (RCR) process using a (b) (4) device to generate the HPC, Cord Blood product. Each unit of HPC, Cord Blood contains a minimum of 9.0×10^8 total nucleated cells with a minimum of 1.25×10^6 viable CD34+ cells, suspended in 10% dimethyl sulfoxide (DMSO) and 1% Dextran 40, at the time of cryopreservation. The total volume of the final product is 25ml, divided in a two compartment cryobag that holds 80% and 20% of the volume. Each HPC, Cord Blood unit is cryopreserved using a controlled rate freezing process and then stored in vapor phase of liquid nitrogen. Final product is tested for identity, purity, sterility, and potency.

The product is indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment. The recommended minimum dose is 2.5×10^7 nucleated cells/kg body weight of the patient.

Cord blood will be collected from (b) (4) medical facilities in (b) (4) from donors who satisfy the requirement of donor testing and screening per 21 CFR 1271. The product will be manufactured at the StemCyte facility. StemCyte has designated contract testing laboratories for donor testing, sterility testing, hemoglobin testing, HLA, and ABO/Rh typing. The final product, HPC, Cord Blood will be shipped using dry shippers that maintain and monitors the temperature at $\leq -150^\circ\text{C}$ throughout the shipping process. The HPC, Cord Blood will be thawed and washed at the clinical site per instruction for preparation for infusion and then administered to the patients.

The CMC review team had extensive interaction with the Applicant during the original BLA review. However, we issued a Complete Response (CR) letter on January 20, 2023, due to several unresolved CMC and CGMP deficiencies related to donor testing and screening, viability assays, flow cytometry assay, process validation, stability studies, and pre-license inspection observations [e.g., corrective, and preventative action (CAPA) report, environmental monitoring (EM) action limits, and several changes made after pre-licensure inspection (PLI)].

The Applicant resubmitted their BLA on November 9, 2023, in response to the CR letter comments, which we reviewed interactively to complete our review. The Applicant adequately addressed all the deficiencies noted in the CR letter. Hence, the CMC review team has concluded that the applicant has established manufacturing processes

and controls capable of producing a consistent drug product of acceptable quality, strength, identity, and purity.

B. Recommendation

The Applicant adequately addressed all the CR Letter comments. The CMC team recommends Approval of this BLA.

Approval:

List of Manufacturing and Testing Facilities:

Facility, Address and Certificate	Responsibility
StemCyte Inc. 13800 Live Oak Avenue, Baldwin Park, CA 91706 FEI#: 3003562296 DUNS#: 162075530	Cord blood collection (by StemCyte personnel), donor screening / eligibility, processing, cryopreservation, release, storage, and testing (Total nucleated cell (TNC) count, (b) (4) and viability of TNCs, CD34+ count & viability, and (b) (4) assay)
(b) (4)	Maternal Blood Infectious Disease Testing, ABO/Rh Typing
(b) (4)	Cord Blood HLA Typing
(b) (4)	Cord Blood HLA Typing
(b) (4)	Cord Blood Product Sterility Testing
(b) (4)	Hemoglobinopathies (b) (4)

- **Post Marketing Requirement or Commitment**

None

- **Inspectional Follow-Up**

None

- **CBER Lot Release**

REGENECYTE is exempt from lot release.

11. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Signature
Saravanan Karumbayaram, M.Pharm., PhD Review Committee Chairperson CBER/OTP/OCTHT/DCT1/CTB1	
Mercy Quagraine, PhD CBER/OTP/OCTHT/DCT1/CTB1	
Fatima Abbasi, MS, MPH CBER/OTP/OCTHT/DCT1/CTTB	
Hanh Khuu, MD CBER/OTP/OCTHT/DHT/HTRS	
Concurred by:	
Irina Tiper, PhD Branch Chief CBER/OTP/OCTHT/DCT1/CTB1	
Eacho Melanie, PhD, RAC Division Director CBER/OTP/OCTHT/DCT1	
Steven Oh, PhD Deputy Office Director CBER/OTP/OCTHT	

Heather Lombardi, PhD Office Director CBER/OTP/OCTHT	
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12. BACKGROUND/HISTORY

StemCyte is a National Marrow Donor Program (NMDP) qualified facility meeting NMDP standards to facilitate transplant of StemCyte cord blood units (CBUs) under IND #7555 Protocol 10-CBA: “A multicenter access and distribution protocol for unlicensed cryopreserved cord blood units (CBUs) for transplantation in pediatric and adult patients with hematologic malignancies and other Indications” (Reference 2.3.S.2). The Applicant started the public stem cell bank operation in 2001 and they have about (b) (4) CBUs in their inventory and more than (b) (4) CBUs distributed for cord blood transplant worldwide.

The Applicant submitted BLA 125764 on January 7, 2022. The product name is Hematopoietic Progenitor Cell, Cord Blood (HPC, Cord Blood), proprietary name – REGENECYTE. This product will be used for 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. This original application was reviewed under non-PDUFA 12-month timeline. Cord blood products are not first in class; hence, an advisory committee was not needed, and the Applicant did not include a voucher application in this or the original submission.

The original submission lacked details and therefore extensive information requests were needed during the review of the BLA. We were unable to resolve all the following notable deficiencies from the original submission:

- a. Deficiencies in donor eligibility testing and screening SOPs were not addressed as recommended.
- b. The process validation in the original submission was deficient. In addition, the Applicant made significant and numerous updates to several SOPs, and the process validation needed to be re-performed incorporating our recommendations and using their updated SOPs.
- c. (b) (4) viability assay validation remained incomplete.
- d. Information about the qualification of cord blood collection sites was not provided.
- e. Shipping validation under (b) (4) temperature extremes was not provided as indicated in their BLA submission.
- f. The flow cytometry based CD34+ cell enumeration assay contained a critical deviation and lacked information about limit of detection.

In addition, the following observations related to FDA form 483 remained unresolved:

- a. SOPs were significantly revised post PLI without showing adequate evidence of effectiveness.

- b. The corrective and preventive actions in a deviation report needed to be updated.
- c. The EM action limits and procedures did not comply to applicable regulations.

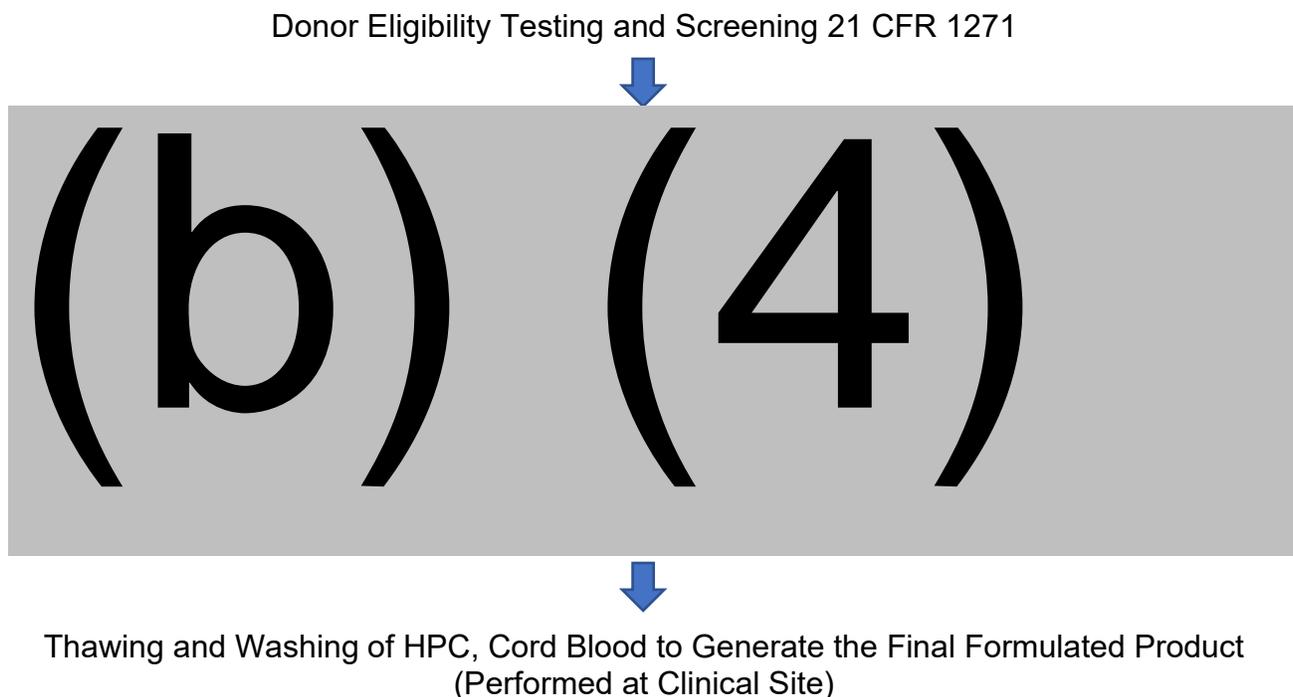
Due to these unresolved CMC, DHT and DMPQ issues, we issued a CR letter on January 20, 2023. The Applicant submitted their resubmission on November 9, 2023. Upon interactive review consisting of multiple information requests and informal calls, the Applicant addressed all the above-noted deficiencies.

13. SUMMARY OF THE MANUFACTURING PROCESS

A. Overview

The StemCyte facility is located at 13800 Live Oak Ave, Baldwin Park, CA. The facility has been used for the distribution of unlicensed cryopreserved cord blood units (CBUs) for transplantation in pediatric and adult patients with hematologic malignancies and other Indications under BB-IND 7555. The manufacturing process for the generation of HPC, Cord Blood is summarized in Figure 1. Please refer to the original CMC review memo for details of the manufacturing process, as this memo focuses on information pertinent to the resubmission review.

Figure 1: Summary of CBU Manufacturing Process



B. Donor Testing and Screening

StemCyte has contracts with (b) (4) hospitals in (b) (4) for the collection of cord blood units (CBUs) and maternal blood specimens. Manufacturing, including processing and storage of HPC, Cord Blood products are performed at the StemCyte, Inc. facility in Baldwin Park, California.

Birth mothers and infant donors are evaluated for relevant communicable disease agents or diseases (RCDADs). Donor screening includes a donor medical history interview and review of the relevant medical records. The donor medical history interview of the birth mother is performed using the NMDP Cord Blood Maternal Risk Questionnaire (NMDP F00316) and NMDP Family Medical History Questionnaire (NMDP F00323). Review of the relevant medical records of the birth mother and the infant donor is documented on three (3) different forms. These activities are performed by StemCyte trained staff or hospital personnel trained by StemCyte. Donor testing is performed on birth mother blood specimens collected within 7 days of the infant's delivery. Testing is performed at (b) (4) in (b) (4). The testing laboratory has a current CLIA certification and registration with the FDA. The donor eligibility determination is performed by the Medical Director of StemCyte.

14. HPC, CORD BLOOD DESCRIPTION AND COMPOSITION

The HPC, Cord blood contains a minimum of 9×10^8 nucleated cells and 1.25×10^6 viable CD34+ cells in a 25ml mixture of 10% DMSO and 1% Dextran 40. Cord blood units are collected in (b) (4) PVC bags that contain Citrate Phosphate Dextrose (CPD), an anticoagulant. Hetastarch (b) (4) is added during (b) (4) processing for volume reduction. The cells are stored in the vapor phase of liquid nitrogen ($\leq -150^\circ\text{C}$). Each HPC, Cord Blood is packaged in a two-compartment cryobag. The larger compartment contains 80% (20ml) of the injectable suspension and the smaller compartment contains 20% (5ml). The rationale for freezing the HPC, Cord Blood product in a two-compartment bag is to allow the removal of the smaller fraction for quality control testing without thawing the larger bag. The HPC, Cord Blood is maintained in a protective steel canister, which is labeled and enclosed in a protective foam thermal sleeve. The units are shipped frozen in special shipping containers (Dry Shipper), which maintain interior compartment temperature at $\leq -150^\circ\text{C}$. The temperature is electronically monitored and recorded during the entire transit time.

- a. Proprietary Name: REGENECYTE
- b. Active Ingredient: Cord Blood Hematopoietic Progenitor Cells
UNII Code: XU53VK93MC
- c. Inactive Ingredients:
 - i. Citrate Phosphate Dextrose (CPD) (NDA (b) (4))
 - ii. 10% DMSO, UNII: YOW8V9698H
 - iii. 1% Dextran 40, UNII: K3R6ZDH4DU
 - iv. (b) (4) UNII: 875Y4127EA

- d. Therapeutic or Pharmacologic Class: Allogeneic cord blood hematopoietic progenitor cells therapy
- e. Dosage Form: Injectable Suspension

15. SPECIFICATION FOR DRUG SUBSTANCE AND DRUG PRODUCT (POST-PROCESSED CORD BLOOD)

The (b) (4) processed CBU (b) (4) considered the drug product (DP).
The drug substance is tested for (b) (4)

Table 1 provides information about the sampling, test methods, and specifications for the post-processed cord blood DS (Section 3.2.S.4.1).

Table 1: Specification for Drug Substance

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(b) (4)

The cryopreserved HPC, Cord Blood drug product is shipped to the clinical sites in dry shippers that maintains the temperature below -150°C. Instruction for use document is available in the prescribing information (PI). In brief, the HPC, Cord Blood, is gently removed from the cassette, and thawed in a 37°C water bath. The HPC, Cord Blood is diluted with wash buffer (Human Serum Albumin and Dextran-40 in Normal Saline), centrifuged, and formulated in equal quantity of wash buffer and sent to bedside for infusion.

16. REVIEW OF APPLICANT RESPONSE TO COMPLETE RESPONSE LETTER COMMENTS

Please Note:

- FDA comment #1 and the review of the Applicant's response was provided by DHT reviewer Dr. Hanh Khuu.
- FDA comments # 2, 3, 6, 7, 8, 9, 11, 12, 15, 18, and 19 and the review of the Applicant's response to these comments were provided and reviewed by Product reviewer Dr. Saravanan Karumbayaram
- FDA comments # 4, 5, 10, 13 and 14 and review of the Applicant's response to these comments were provided reviewed by CMC reviewer Dr. Mercy Quagraine.
- FDA comments # 16 and 17 and the review of the Applicant's response to these comments were provided and reviewed by CMC reviewer Ms. Fatima Abbasi
- FDA comments # 20-23 and the review of the Applicant's response was provided by DMPQ reviewer Dr. Xiuju Lu. Please refer to the attached DMPQ concurred review memo for the review of their discipline comments.

The FDA CR comments are italicized throughout this memo.

FDA CR Comment #1

With reference to donor screening, donor testing and donor eligibility (DE) determination, we sent you multiple information requests (IRs) on the following dates: March 22, 2022, May 11, 2022, June 2, 2022, August 1, 2022, October 6, 2022, and November 10, 2022. However, your response to those IRs did not completely address the concerns we raised, and we need additional information from you to complete the review of this section. Therefore, please address the following.

- a. Regarding donor medical history interview in Section 3.2.S.2.2.1.1, you indicate that the medical history interview of the birth mother may be completed 30 days after the cord blood collection date. Please clarify whether donor medical history questions are posed to the birth mother, such that the responses to the questions are relevant to the date of cord blood unit (CBU) collection.*

Applicant’s Response

Reference: 12.1.003-PU; 12.3.017-01-PU and 3.2.S.2.2.1.1

StemCyte submitted a revised description of the donor screening process and procedure in which the birth mother’s medical history interview will be performed within 7 days before or after cord blood collection date.

Reviewer Assessment: BLA Section 3.2.S.2.2.1.1 Donor Screening and SOP 11.1.022-PU Review of Donor Records for Donor Eligibility Determination was revised: “the medical history interview of the birth mother is conducted within 7 days before or after cord blood collection. If the medical history interview is conducted more than 7 days before the collection, any changes in the medical history are obtained and documented at the time of [cord blood] collection on the Maternal Health History Update Form and reviewed by the medical director for acceptability.” The revised procedure is acceptable.

- b. With reference to the review of relevant medical records of the birth mother and infant donor, SOP 11.1.022-PU outlines the procedures for DE determination. Furthermore, SOP 12.1.003-PU outlines the procedures for review of medical records for risk factors for, and clinical evidence of, Relevant Communicable Disease Agents or Diseases (RCDADs). However, these Standard Operating Procedures (SOPs) do not describe whether a cord blood donor is determined eligible if a “YES” response is documented for any item in Section B (pre-delivery / delivery events or complications and pregnancy history) and Section C (infant assessment) on the Collection and Delivery form (12.3.008-02-PU). Please revise the SOP to describe how each item with a “YES” response is evaluated when making a DE determination and submit the updated document.*

Applicant’s Response

Reference: 11.1.013-PU; 11.1.022-PU; 11.2.022-PU; 11.2.022-01-PU; 11.3.022-01-PU; 11.3.022-02-PU; 12.1.003-PU; 12.1.009-PU; 12.3.008-02-PU; 12.3.017-01-PU;

11.1.013-PU; 11.1.022-PU; 11.2.022-PU; 11.2.022-01-PU; 11.3.022-01-PU; 11.3.022-02-PU; 12.1.003-PU; 12.1.009-PU; 12.3.008-02-PU and 12.3.017-01-PU StemCyte explained that SOP 11.1.013-PU provides individual screening criteria for each question asked of the birth mother on the NMDP questionnaires, which includes how to evaluate “YES” responses for questions related to the screening for RCDADs as well as heritable disease risk captured in the Family Medical History Questionnaire. In addition, StemCyte revised SOP 12.1.003-PU and SOP 12.1.009-PU to describe steps to be taken when the “YES” response is recorded.

Reviewer Assessment: SOP 11.1.013-PU addresses the donor medical history interview questionnaire. SOP 12.1.003-PU and 12.1.009-PU address review of the forms that document review of relevant medical records. Additional details below in response to comment 1c. The revised SOPs are acceptable.

- c. *The Collection and Delivery Form (12.3.008-02-PU) includes the following statement: “maternal hospital medical records have been reviewed for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases including HIV, HBV, HCV, syphilis, HTLV, WNV, vaccinia, Zika virus, and human transmissible spongiform encephalopathy, including vCJD”. The same statement is included on the Maternal Health History Update form (12.3.017-PU) and the Maternal Blood Sample Collection and Medical Records Review form (12.3.017-01-PU). It is unclear how the person (healthcare provider or StemCyte staff) that completes this section is informed which risk factors, clinical evidence, or physical evidence of RCDADs they evaluate. Please submit an SOP or instructions that you provide to healthcare providers and StemCyte staff for review of this information.*

Applicant’s Response

Reference: 11.2.022-PU; 11.3.022-01-PU; 12.3.017-01-PU

Two (2) job aids were created “to assist the health historian and medical records reviewer in evaluating individual responses to questions and to aid in performing the medical records review for evidence of RCDADs.”

Job Aid 11.2.022-PU Donor Screening Tool for RCDADs

Job Aid 11.2.022-01-PU Physical Examination Supplemental

Reviewer Assessment: Though StemCyte created the new job aids, these job aids were not included in the instructions for staff to refer to when performing the medical records review. In response to an information request (Amendment 37), the applicant revised the form instructions provided on the reverse side of the relevant forms (collection and delivery form, maternal blood sample collection and medical records review form, and maternal health history update form) to include the job aids. The new procedures and revised forms are acceptable.

- d. *With reference to the information provided in BLA Section 3.2.S.2.2, about donor testing, you indicate that the birth mother’s specimen is tested for treponemal*

specific assay for syphilis (b) (4) Please note that if the birth mother tests reactive using a treponemal specific assay for syphilis, the donor should be determined ineligible regardless of any subsequent confirmatory test result (refer to 21 CFR part 1271.80(d)(1) and section VI.A of the 2007 Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/PS), <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM091345.pdf>.

In all donor testing-relevant SOPs and forms, you state that a donor is eligible if “reactive syphilis with negative confirmatory testing.” For example, form 11.3.022-01-PU indicates that a donor with “reactive syphilis with negative confirmatory testing” is determined eligible and the CBU meets criteria for licensure. The statements “reactive syphilis with negative confirmatory testing” and “non-treponemal test for syphilis when specific treponemal confirmatory test is negative” in your documents, would only apply if you were utilizing a non-treponemal screening test for syphilis. Please revise all relevant sections of the BLA, SOPs and forms to specify that a donor with reactive test for syphilis (treponemal specific) is ineligible.

Applicant’s response

Reference: 11.3.022-01-PU and section 3.2.S.2.2.1.1

StemCyte provided the following response: “The testing vendor previously offered a non-treponemal assay but revised their testing policy to include a treponemal-specific assay. When this change was implemented, not all affected documents were identified and updated. A careful review of all related or documents impacted by this changed and revisions have been made to reflect the use of only treponemal-specific assays. Donors who test positive are deferred from donation.”

Form 11.3.022-01-PU Donor Records Review Summary was revised to remove references to specific tests for syphilis.

Reviewer Assessment: The revised document is acceptable.

e. *Regarding the final DE determination:*

It is unclear whether the DE determination is made by the Medical Director or designee before the HPC, Cord Blood is listed in the National Marrow Donor Program (NMDP) searchable inventory. In SOP 16.1.003-UN, the purpose of the SOP is “provide an overview of the review process to determine if a public cord blood unit is eligible for transplant.”

SOP 16.1.003-UN, Section 2 states the following:

- *“Applicant performs this donor eligibility determination during what we call the “2nd Review” of the donor/cord blood file folder. (See 16.1.006-UN (#G06)) At the end of this review, the donor eligibility determination and 2nd review are*

documented. If the donor is eligible and the 2nd review is satisfactory, the donor is made available for search in the NMDP Registry.”

- *“2nd review of donor’s file folder. The 2nd review by the Medical Director or designee is the final step in donor eligibility. (See 16.1.006-UN (#G06), Product Review –Public Bank) This review covers all the information currently in the file folder, including donor history questions, maternal testing, and cord blood testing results. The results of this review and documentation of this review indicate that the cord blood unit is no longer in quarantine and is now in permanent long-term storage.”*

According to the above information, it appears HPC, Cord Blood is listed in the NMDP registry after the documentation of the DE determination by the Medical Director or designee in the “2nd Review.” However, we note the following discrepancies:

- *Review flowchart submitted in Amendment 5 does not indicate that the “Final Donor Eligibility and Review” is performed by the Medical Director or designee. The flowchart indicates that the “MD Review” is completed before the HPC, Cord Blood is released for transplantation.*
- *The revised SOP 11.1.022-PU, section 2- Donor Eligibility Determination (Amendment 31) states “All cord blood units remain in quarantine status until the donor eligibility determination has been completed and determined to be eligible or ineligible by the responsible donor eligibility specialist.” It appears the HPC, Cord Blood may be released from quarantine by the “donor eligibility specialist” before review and documentation of DE determination by the Medical Director or designee.*

Please address the following and submit the revised documents:

- Please confirm that the final DE determination is made and documented by the Medical Director or designee before the HPC, Cord Blood is released to the NMDP’s searchable inventory and clearly describe the steps in the SOPs.*
- If the DE determination is performed by a responsible person other than the Medical Director, please describe their qualification and medical training.*
- According to SOP 16.1.003-UN CBUs from “ineligible” donors (e.g., positive for anti-HBc) can be designated as “transplantable” and made available for transplantation if there is an urgent medical need. Please note, that in case of an urgent medical need, such units may be made available for transplant under an investigational new drug application (IND). Please revise and submit the SOPs and forms that clearly describe that such units do not meet acceptance criteria for licensure.*

Applicant's Response

Reference: 01.1.011-PU; 16.1.003-PU; 16.1.006-PU; 11.1.022-PU

StemCyte states that the Medical Director performs the donor eligibility determination by completing the Declaration of Donor Eligibility Form 11.3.022- 02-PU. StemCyte states “No Donor Eligibility determinations are made by any individual other than the Medical Director.” (Response to CR Letter dated 20 January 2023).

In addition, StemCyte states “SOP 16.1.003-UN was updated as a new document specific to public CBUs only (SOP 16.1.003-PU), clearly stating that ineligible units are not able to be licensed but may be made available for transplant under an IND and documentation of urgent medical need from the transplant physician.”

Reviewer Assessment: StemCyte revised their process for review of batch records and product release with the following:

- 1 - StemCyte provided a revised flowchart “Donor Records Review and DE Determination Process Flowchart”. The flowchart delineates clerical review, donor record review, DE determination and batch release.
- 2 - Descriptions of manufacturing process and process controls of the drug substance (3.2.S.2.2) and the drug product (3.2.P.3.3) were “revised/rearranged to better reflect the point(s) at which donor suitability and screening procedures are employed at collection sites during procurement. Language regarding determination of donor eligibility was removed from 3.2.S.2.2 [drug substance] and inserted into 3.2.P.3.3 [drug product].”
- 3 - StemCyte revised their description of the donor records review process and donor eligibility determination process. StemCyte created new forms and revised SOPs to delineate review processes, DE determination, and release for distribution. The donor record review is documented separately from the declaration of donor eligibility. The summary of records form (16.3.007-04-PU) was created as part of the revised record review process. The communicable disease tests listed in a table on the form was incorrect. The revised form (revision 2) was submitted in Amendment 37. The new procedures and revised forms are acceptable.

- f. *According to information submitted in amendments, we understand the following documents are being revised. Please submit the following final SOPs and forms:*
 - i. SOP 01.1.020-UN Chain of Custody for StemCyte Cord Blood Bank
 - ii. SOP 04.1.082-PU Public Shipper Use and QC/PM
 - iii. FORM 04.3.082-PU Shipper Daily QC/PM
 - iv. SOP 10.1.008-PU NMDP Product Requests
 - v. SOP 11.1.008-PU Donor Demographic Information and Health History Forms
 - vi. SOP 12.1.006-PU Ex Utero Cord Blood Collections-Public
 - vii. SOP 13.1.005-UN Maternal and CB Specimen Processing
 - viii. SOP 14.1.010-PU Packing and Shipping Samples to (b) (4)
 - ix. SOP 16.1.003-UN Availability of Public Cord Blood Units for Transplantation and Distribution-Shipping

Applicant's Response

Reference: 01.1.020-UN; 04.1.082-PU; 04.3.082-PU; 10.1.008-PU; 11.1.008-PU; 12.1.006-PU; 13.1.005-UN; 14.1.010-PU; 16.1.003-UN

StemCyte submitted revised documents.

Reviewer comment: 01.1.020-UN Chain of Custody for StemCyte Public Cord Blood Bank – Revision 2 was submitted in Amendment 35 in response to the CR Letter. Revision 3 was revised to include donor eligibility determination and product review processes as part of an information request and submitted in Amendment 36. Other documents submitted as requested are acceptable.

FDA CR Comment #2

In your August 24, 2022, response to our August 1, 2022, IR, you provided information limited to (b) (4) CBU collection sites and intend to qualify new CBU collection sites according to SOP 01.1.003-UN Critical Supplier Qualification. However, this SOP contains information only on material supplier qualification and not CBU collection sites. While Quality Manual 01.1.001-UN, v.9 contains some information on qualification of collection procedures, it does not entail the qualification of CBU collection sites. Given that you have not outlined the procedures used for the qualification of collection sites, we are unable to determine how you qualify collection sites. Therefore, please provide a detailed narrative and protocol on the procedures used for qualification of CBU collection sites, including new collection site(s).

Summary of the Applicant Response

Reference: 12.1.001-02-PU; 12.1.001-03-PU; 12.3.001-02-PU.

They have generated SOPs 12.1.001-02-PU titled “Fixed Collection Site Qualification.” 12.1.001-03-PU Qualification of Prospective New Public Cord Blood Collection Site and Form 12.3.001-02-PU Fixed Collection Site Suitability Checklist to satisfy the requirements for collection site qualification. The above SOPs and form provide the requested details. They inspect the collection site for the following attributes and check the suitability using the Fixed Collection Site Suitability Checklist.

- a. General – designated storage and preparation area: secure access, temperature-controlled storage area
- b. Collection area: secure access, appropriate size for collection, sink/drain access, adequate lighting and ventilation, adequate storage of equipment.
- c. Biohazards: available waste/sharps containers, proper storage, and signage
- d. Chemicals/Reagents: spill kits, cleaning, appropriate storage requirements
- e. Electrical: Adequate outlets, equipment location, tagged defective equipment
- f. Safety: Doors can remain closed, clear passageways/hallways, first aid kits and fire extinguisher available, exit signage visibly posted.
- g. Authorized access to shipping containers

h. Evaluation of logistics related to courier pickup and delivery.

Collection site qualification process includes an agreement between the participating centers and StemCyte regarding space for collection, and storage of CBU, site suitability inspection to verify collection site floor plan, equipment, supplies, and reagents required and prevention of contamination.

Collection site qualification process will be performed per Collection Site Qualification protocol document 12.1.001-03-PU, that was submitted for review. This protocol contains procedures used for qualification of collection site, that includes installation, operational and performance qualification.

The procedures for cord blood collection are provided in the following documents:

- Collection Agreement
- Training Program Agreement
- Facilities for ex-utero collection, storage of supplies, storage of collected CBUs, and shipment of CBUs to StemCyte
- Informed Consent
- Obtaining maternal and infant data
- Obtaining maternal blood sample

Installation Qualification document provides details about the

- Agreements
- Staffing
- Training plan
- Facility
- Employees safety
- Temperature monitoring
- Documentation

Operational Qualification document provides details about the following:

- Use of collection supplies
- Consenting
- Cord blood collection
- Labeling
- Safety
- Maternal and infant data completion
- Review of relevant medical records (maternal/infant delivery records)
- Storage of supplies and cord blood units
- Shipping of units and blood samples to StemCyte

Performance Qualification includes the following:

- (b) (4)

- (b) (4)

Reviewer Comment:

SOP 12.1.001-02-PU titled, “Fixed Collection Site Qualification, uses more than one terminology to identify Cord blood Unit (CBU). Generally, in this BLA, the CBU that is collected from donors are labeled as CBU and the final product is labeled as HPC-Cord Blood. However, the Applicant interchanges CBU and HPC-Cord Blood throughout this SOP, and that should be corrected. This issue was resolved via IR.

Information Request Sent on January 26, 2024: *With reference to SOP 12.1.001-02-PU, you have employed multiple terms to refer to cord blood unit (CBU). In your Original BLA, the CBUs that is collected from donors are denoted as CBUs, while the final product (plasma and red cell reduced CBU) is labeled as HPC, Cord Blood. However, in this SOP, CBU and HPC, Cord Blood has been used interchangeably for cord blood units collected from donors. Please ensure consistent terminology in this SOP and submit the revised version.*

Applicant Response Received on February 8, 2024: SOP 12.1.001-02-PU has been revised with the correct terminology for collected cord blood from donors at collection sites as Cord Blood Units or CBUs. References to the final processed red cell reduced HPC, Cord Blood product were removed as the procedure only addresses procurement of fresh cord blood and was not intended to be used interchangeably with final product designation of HPC, Cord Blood.

Reviewer Assessment of Applicant Response to IR: The applicant has corrected the terminology in SOP 12.1.001-02-PU, and it is acceptable.

Reviewer Assessment of Applicant Response to Comment #2: The response provided by the Applicant details the procedures used for qualification of CBU collection sites, including new collection site(s). Their response is acceptable.

FDA CR Comment #3

You have not provided the protocol and report for the entire process validation (PV) beginning with CBU collection through thawing and washing of the product using the validated SOPs. During the original BLA review period, as a result of your responses to our numerous IRs, you significantly modified the methods used in the manufacture and quality control testing for cell viability, CD34 count, and sterility of HPC, Cord Blood. In addition, to address the below Complete Response comments, additional modifications to PV may be necessary. PV should provide objective evidence that the process consistently produces the product meeting its predetermined specifications. Given that you revised your methods for several product attributes and have not provided a PV protocol report covering the entire manufacturing process, we cannot determine if you can consistently manufacture HPC, Cord Blood with your updated manufacturing process. Please perform and provide a complete PV report with protocol for your entire manufacturing process addressing the following and incorporating your updated SOPs:

- a. *It appears that the CBUs used in your PV study were not consecutively collected and you may have provided data only on CBUs meeting specifications rather than consecutively collected CBUs. Please submit a revised/updated process validation protocol and report. The validation protocol should provide a detailed narrative of what will be executed and the pre-specified criteria (both in-process and final specifications) to be met. The process validation should cover collection, manufacture/processing, as well as the thawing and cryoprotectant removal post thaw from consecutively collected CBUs to demonstrate that you are able to consistently manufacture and thaw those HPC, Cord Blood units that meet the in process and final product specifications. The validation report should contain a summary of the validation results after executing the validation protocol. Please provide a revised validation report.*
- b. *In your PV study report, please include tables that contain acceptance criteria and results for pre-processing CBUs, post-processing HPC, Cord Blood and post-thaw and wash HPC, Cord Blood drug product.*
- c. *Please list deviations, if any, noted (including the CBUs that failed the in-process and final release criteria) during the entire PV, and summarize your plans to prevent such deviations in the future.*

Summary of Applicant Response

References: SN0036 Response to CRL dated 20 January 2023; PV-0016-25 Manufacture of Public Donated Placental/Umbilical Cord Blood Process Validation Protocol; PV-0016-25 Validation Deviation Report; 13.3.001-01-UN Red Cell Reduction Cord Blood Processing Worksheet; 13.3.002-01-UN Cord Blood Processing Worksheet; PVSR-0016-25 Process Validation Summary Report.

Please Note: Since the sections a-c in the FDA comment are subsets of the process validation, we combined the review of Applicant response to sections a-c and reported here.

- Donor consent is received before collection of cord blood per ex-utero collection method (SOP 12.1.006-PU) and Ex+ Cord Blood Collection Method (SOP 12.2.006-3-PU) the Collection and Delivery Form (12.3.008-02-PU) is filled with relevant information. Donor testing and screening are performed, and they consecutively collected (b) (4) CBUs between (b) (4) for process validation.
- CBUs with initial (b) (4) (b) (4) (including collected CB, CPD, and the collection bag with tubing and a needle) are transported to StemCyte facility for further processing.

- The received CBUs are examined to determine if they met the pre-processing criteria (b) (4) per SOP 13.1.026-PU.
- Out of (b) (4) CBUs (b) (4) of them passed the pre-processing acceptance criteria.
- From the (b) (4) CBUs, (b) (4) of them were used for processing using (b) (4) processing system per SOP 13.1.025-PU and cryopreserved using the (b) (4) (b) (4) cryoprotectant and used control rate freezing process per SOP 13.1.011-01-PU and SOP 13.1.004-UN to cryopreserve the cells.
- The post-processing samples are tested for total nucleated cell counts (TNC) per SOP 14.1.039-PU, cell viability per SOP 14.1.040-PU, CD34 count per SOP 14.1.023-UN, (b) (4) assay per SOP 14.1.015-UN, and sterility of HPC, Cord Blood per SOP 14.1.005-UN.
- The cryopreserved CBUs were thawed and washed per SOP 17.1.005-UN. The post thaw samples are tested for TNC, cell viability, CD34 count, (b) (4) assay, and sterility per SOPs as indicated above. Acceptance criteria for process validation is shown in Table 2.

Table 2: Acceptance Criteria

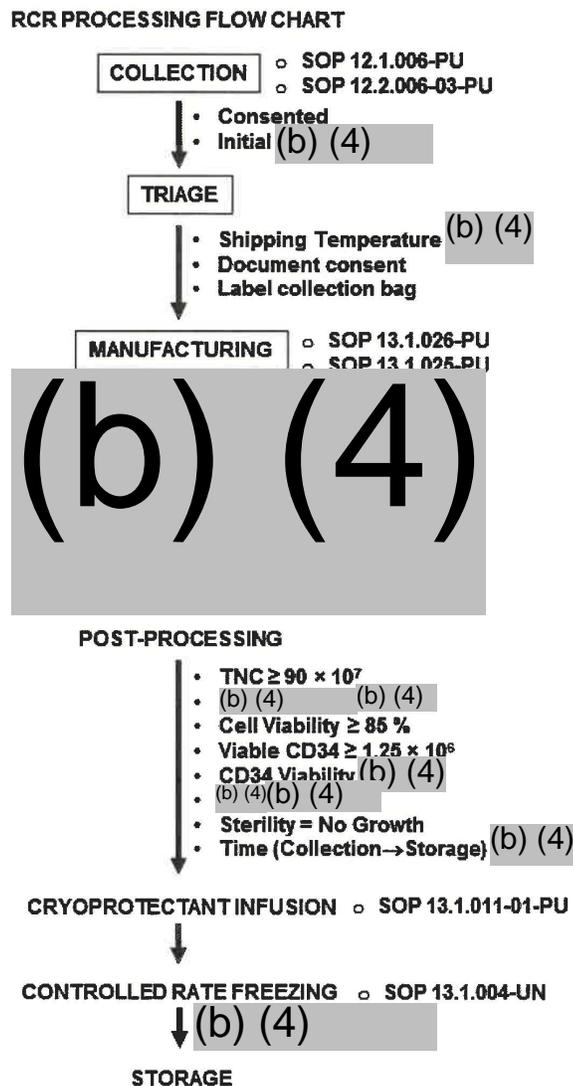
Requirements ID	Acceptance Criteria
#1	<ul style="list-style-type: none"> • Collection: Signed Consent Form • Collection: Initial (b) (4) of CBU (b) (4)
#2	<ul style="list-style-type: none"> • Triage: Shipping Temperature: (b) (4) • Triage: Collection Bag: intact and no sign of contamination and leakage • Triage: Document and labeling - completed
#3	<ul style="list-style-type: none"> • Pre-processing: (b) (4) of CBU (b) (4) • Pre-processing: (b) (4) • Post-processing: Cell Viability $\geq 85\%$ • Post-processing: TNC $\geq 90 \times 10^7$ cells • Post-processing: (b) (4) • Post-processing: CD34 Viability (b) (4) • Post-processing: Viable CD34 $\geq 1.25 \times 10^6$ cells • Post-processing: (b) (4) • Post-processing: Sterility Testing: No Growth (Negative) • Post-processing: Elapsed time from collection to storage (b) (4)

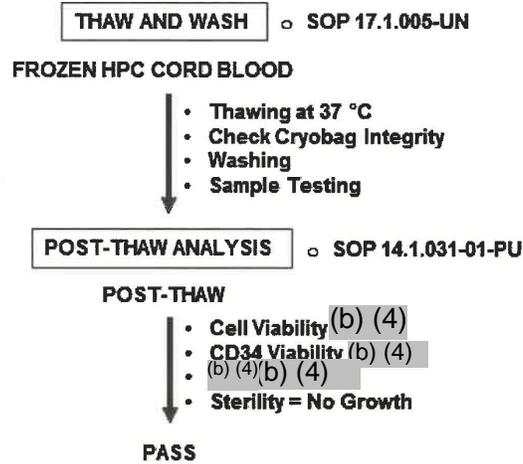
#4	<ul style="list-style-type: none"> • Post-thaw: Integrity of a Cryobag: Intact • Post-thaw: Viability CD34 (b) (4) • Post-thaw: Cell Viability $\geq 70\%$ • Post-thaw: Total (b) (4) Assay (b) (4) • Post-thaw: Sterility Testing = No Growth (Negative)
#5	<ul style="list-style-type: none"> • Passive Air and Surface Monitoring: (b) (4) in a BSC • Laboratory Microbial Surface Monitoring: (b) (4)

Reviewer Comment: The acceptance criteria are based on validation of the applicable assays, and they are acceptable.

Process validation was performed per the steps shown in the flowchart in Figure 2.

Figure 2: RCR Process Validation Flow Chart





Reviewer Comment: In section 7.0 of PV-0016-25, the Applicant provided the list of SOPs and forms that was used to execute the process validation; they are acceptable.

CBU Collection: CBUs with (b) (4) and (b) (4) of (b) (4) meet minimum pre-processing acceptance criteria for processing to manufacture of HPC, Cord Blood. CBUs that did not meet this criterion was used for research and training purpose. Table 3 shows the overview of CBUs collected for process validation.

Sampling plan for Process Validation: Pre-processing sample are collected to perform (b) (4) testing. Post processing sample are collected for CD34 enumeration, cell viability and (b) (4) assay. (b) (4) are collected for (b) (4) testing. Sterility testing is also performed on samples collected from post-thaw and washed HPC, Cord Blood.

Table 3: Overview of CBUs collected between (b) (4)

(b) (4), (b) (6)

Reviewer Comment: Of the (b) (4) CBUs, (b) (4) CBUs did not meet the minimum (b) (4) criteria of (b) (4) reportedly due (b) (4) Table 4 shows the CBUs used for pre-processing (b) (4)

Table 4: CBUs Used for Pre-processing (b) (4)

(b) (4), (b) (6)

Reviewer Comment: Of the (b) (4) CBUs, (b) (4) CBUs passed the pre-processing (b) (4) (b) (4) and of the (b) (4) CBUs, (b) (4) passed the pre-processing (b) (4)

The (b) (4) CBUs that passed the pre-processing (b) (4) (b) (4) were processed using the (b) (4) RCR method (SOP 13.1.026-PU) and cryopreserved and stored at temperature below -150°C.

The post-processing acceptance criteria is shown in Table 5, and a summary of post-processing testing results from (b) (4) manufactured HPC, Cord Blood is shown in Table 6.

Table 5: Post-Processing Acceptance Criteria

Cell Viability	≥85%
TNC Count	≥ 90 X 10e7
(b) (4)	(b) (4)
CD34 viability	(b) (4)
CD34 Count	≥1.25 X 10e6
(b) (4)	(b) (4)
Sterility	No growth
Elapsed Time	(b) (4)

Table 6: Summary of Post-processing Testing Results from (b) (4) manufactured HPC, Cord Blood.

(b) (4), (b) (6)

(b) (4), (b) (6)

Reviewer Comment: All the (b) (4) CBUs passed the post-processing acceptance criteria.

Post Thaw analysis: The Applicant used (b) (4) cryopreserved (b) (4) of the (b) (4) HPC-Cord Blood for their post thaw analysis per SOP 17.1.005 Thaw and wash for RCR units. The post thaw analysis and acceptance criteria are shown in Table 7, and the summary of post-thaw testing results from (b) (4) thawed HPC, Cord Blood are shown in Table 8.

Table 7: Post-Thaw Acceptance Criteria

Integrity of a Cryobag	Intact, no leakage
Cell Viability	≥70 %
CD34 viability	(b) (4)
Total (b) (4)	(b) (4)
Sterility	No Growth

Table 8: Summary of Post-Thaw Testing Results from (b) (4) Thawed HPC, Cord Blood Units

(b) (4), (b) (6)

Assessment of Applicant Response: *The Applicant has provided the protocol and report for the entire process validation (PV) beginning with CBU collection through thawing and washing of the product. Review of the validation report shows that they were able to consistently manufacture the product meeting pre-determined specifications. The study report includes tables with acceptance criteria and results for pre-processing CBUs, post-processing HPC, Cord Blood and post-thaw and wash HPC, Cord Blood drug product. Regarding the deviations, of the (b) (4) CBUs, (b) (4) CBUs passed the pre-processing (b) (4) and of the (b) (4) CBUs, (b) (4) passed the pre-processing (b) (4). The CBUs that did not meet the acceptance criteria (collection, pre-processing, postprocessing, and post-thaw criteria) were listed in the deviation reports (VDR-PV-0016-25-DE01 and VDR-PV-0016-25-DE02). The failure to pass the specified requirement for CBU (b) (4) is donor specific, and it is not due to failure in the process. Of note, in general, the noted failure rate appears commensurate to other BLAs that have reported upwards of 50% failure due to CBUs not meeting the minimum (b) (4) criterion in discussion with Mercy Quagraine. One observation she noted was that cord blood (b) (4) tend to be lower in minority births. The Applicant has responded to all the 3 sections (a-c) of the FDA CR comment #3. The Applicant's response is acceptable.*

FDA CR Comment #4

In your October 31, 2022, response to our IR dated October 18, 2022, you submitted a

revised (b) (4) viability SOP 14.1.040-PU and assay validation report, without providing any supporting narratives on what was revised or an explanation for the changes. The procedures in the revised SOP 14.1.040-PU and the validation report do not match. Your (b) (4) viability assay does not provide assurance that you would be able to reproducibly perform the assay. Please provide a revised (b) (4) validation protocol and report. The validation protocol should contain a detailed description of what will be executed for all the parameters assessed and the pre-specified criteria that would be met. The validation report should contain a summary of the results obtained after execution of the validation protocol, any deviations encountered and their resolutions as well as conclusions of the validation study. In addition, the study should address the following:

- a. Please provide a summary of the changes you implemented and the rationale for these changes to the revised (b) (4) viability assay.

Applicant Response

Reference: SOP 14.1.040-PU

1. A (b) (4) step has been added to the post-processing sample preparation prior to (b) (4) (b) (4) The revisions to the (b) (4) assay (SOP14.1. 040.PU (3) included the (b) (4)

2. Section 6 Step ^{(b) (4)} has been revised to include (b) (4)

(b) (4)

Note: Post-processing sample is (b) (4)

3. The post-thaw viability testing has been included in Section 6.0 Procedure of the (b) (4) Testing SOP 014-1.04-PU.

Procedure for Post-Thaw sample testing: (b) (4)

4. The post-thaw viability specification has been updated to $\geq 70\%$ from (b) (4). The post-processing viability specification is $\geq 85\%$ (unchanged).

Reviewer Assessment: The Revised (b) (4) SOP 014-01-04-PU (Revision 3) contains all the proposed changes. The comment has been adequately addressed and the revisions are acceptable.

b. In the revised (b) (4) viability assay validation report, you did not establish a limit of quantitation of 0% viability. Please establish a limit of quantitation for the (b) (4) viability assay. A 0% viability can be attained by methods such as heat treatment of cells in a $\geq 60^\circ\text{C}$ water bath.

Applicant response

Reference: MV-0079-04

0% viability was established by putting the cell sample in the (b) (4). Zero percent (0%) viability was achieved.

Reviewer Assessment: A 0% viability was established in the validation. This response is acceptable.

c. Please submit the (b) (4) viability assay validation report with data obtained with thawed cord blood samples. The validation report should include the validation protocol, as well as a detailed description of how the assay was executed and the pre-specified criteria. The validation report should also contain a summary of the results in tabular form and a discussion of any deviations encountered.

Applicant Response

Reference: MV-0079-04; MVSR-0079-04

Please see MV-0079-04 (protocol) and MVSR-0079-04 (report) that assesses the viability of post-processing and post-thaw samples (b) (4).

Reviewer Assessment: After the review of the validation documents MV-0079-04 and MVSR-0079-04, we found that the procedures followed were correct. However, there were some contradictory statements in the description of the assay and not the procedure itself and, thus, did not impact the assay/testing itself. The following information request was sent requesting the Applicant to revise the description to revise any contradictions.

Information Request Sent on January 26, 2024: Regarding your responses to our comment 4 on the (b) (4) assay, please address the following:

a. The description of the assay in the (b) (4) validation protocol, MV-0079-04 Section 5.0, contradicts the description in section 5.1 of the same protocol and also the description of the assay in the (b) (4) SOP 14.1.040-PU. According to Section 5.0 of MV-0079-04 of the validation protocol, (b) (4)

In Section 5.1 of MV-0079-04 and also in the revised SOP 14.1.040-PU (revision 3), you state that (b) (4)

Section 5.1 of validation protocol (MV-0079-04) matches the (b) (4) SOP 14.1.040-PU. Please revise and submit.

b. Section 3.0 of the (b) (4) validation report MVSR-0079-04, has a similar description of the (b) (4) assay as in Section 5.0 of MV-0079-04 which contradicts the description in SOP 14.1.040-PU (see a. above). Please revise so only the correct description remains.

Applicant Response Received on February 8, 2024: The Applicant response adequately addressed the information request. Please see the review of the validation report below.

Summary of Validation study (Linearity study; precision; reproducibility)

(b) (4)

Results: (b) (4)

Note: In a January 26, 2024, follow up request for information, and response received February 8, 2024, Table 9 was revised for clarity in accordance with the information request. The revised Table 9 is appended below.

The specific information requested was as follows:

Information Request Sent on January 26, 2024: *Regarding your responses to our comment 4 on the (b) (4) assay, please address the following: For Table 9, Summary of the Linearity studies, please revise the table and change the (b) (4) to ‘%Viability’ for clarity since it is cell viability which is being assayed. The **expected viabilities** are prepared by (b) (4)*

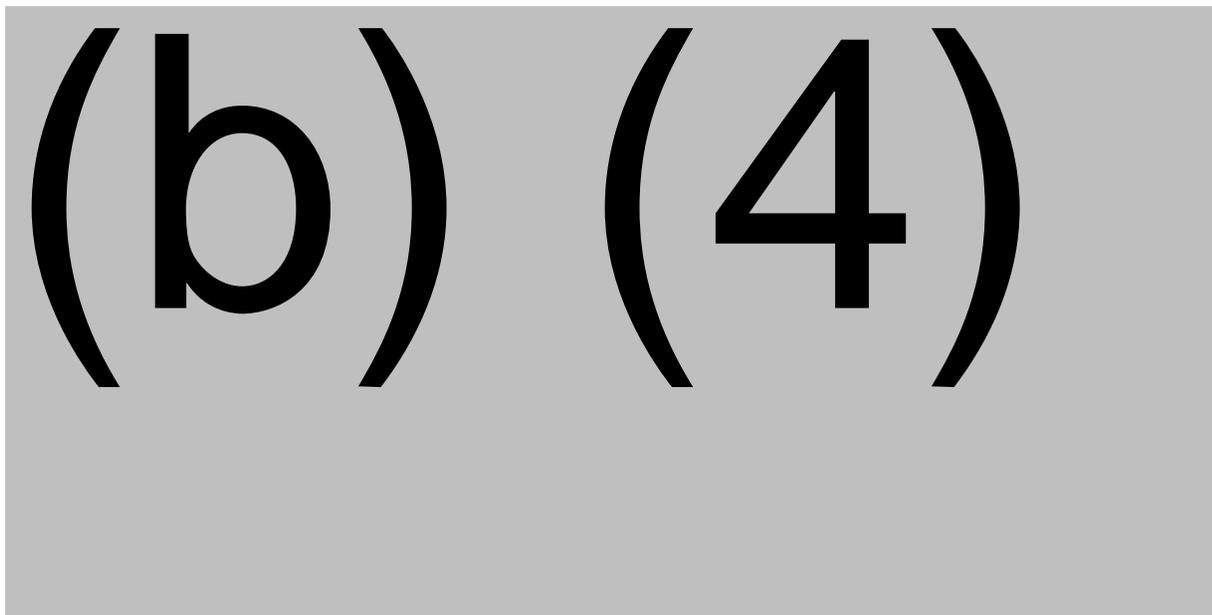
*The **observed viabilities** are the values read on the (b) (4) by the technicians and entered in Table 1. Please revise your table accordingly for clarity.*

Revised Table 1 per February 8, 2024, responses to January 26, 2024, IR:

Table 9: Post Processing Summary

(b) (4), (b) (6)

Figure 3: Post Processed CBU (b) (4), (b) (6)



This figure provides graphical representation of plotting different (b) (4) post processed CBU with (b) (4) to show that the Applicant is able to evaluate (b) (4) (b) (4) in post processed CBU. Applicant provided data for (b) (4) other CBU lots (b) (4), (b) (6) (b) (4), (b) (6) that look similar to the representative Figure 3. R2 specification of (b) (4) was met in the linearity studies.

Reviewer Assessment: The (b) (4) validation studies are adequate and acceptable. The appropriate revisions have been made to the protocols. Linearity has been demonstrated.

- d. *You established the post-thaw viability for total nucleated cells (TNC) at (b) (4). The post-thaw TNC viability of (b) (4) does not meet the criterion of $\geq 70\%$ for post-thaw TNC viability described in FDA's 2014 guidance titled, "Biologics License Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System" (Cord Blood Licensure Guidance) available at cord blood BLA guidance (<https://www.fda.gov/media/86387/download>). Please update your post-thaw TNC viability criterion to reflect the acceptable level of 70% or greater, as described in the guidance.*

Applicant Response

Reference: SOP 14.1.040-PU.

The post-thaw viability has been updated to $\geq 70\%$ (see section 7.0 of SOP 14.1.040-PU)

Reviewer Assessment: The Applicant has updated the post-thaw TNC viability criterion to reflect the acceptable level of 70% or greater. Their response is acceptable.

Since your process validation and stability studies were conducted with the previous unrevised SOP, please conduct these studies with the revised viability assay SOP and submit this data.

Applicant Response

Reference: PV-0016-25, PVSR-0016-25 and CSR-088-01, CSSR-0088-01

See Processing Validation (PV-0016-25 and PVSR-0016-25) and Stability Study (CSR-0088-01 and CSSR-0088-01). See response to 4e for validation summary.

Reviewer Assessment: Applicant has conducted the requested studies using updated SOPs. The response is acceptable.

FDA CR Comment #5

With reference to the (b) (4) assay validation, please address the following:

- a. *The section titles and the descriptions in SOP Validation ID: CSR-0044-02 and validation report CSSR-0044-02 are not consistent with the respect to the scope of the SOP.*
 - i. *In your SOP Validation ID: CSR-0044-02, Section 1.0, you state that “this characterization study” is applicable to (b) (4) assay performed at StemCyte Inc,” and in Section 3.0, you describe the scope of the validation as “the equipment/systems and all associated components listed in section 1.”*
 - ii. *In the Validation Summary Report: CSSR-0044-02, Section 1.2, you state that “This Characterization Study is applicable to (b) (4) assay performed on post-processing sampling of red cell reduced RCR Cord Blood Units CBUs.”*

Please revise your (b) (4) assay validation sections, so that the narrative details provided in the described sections match/reflect the respective titles.

Applicant Response

Section 1 Equipment/System Identification, Section 2 Purpose, Section 3 Scope of the as (b) (4) validation protocol and reports are revised as requested. The revised documents have ‘ADD1’ added to their titles. The revised documents are the (b) (4) validation protocol: CSR-0044-02-ADD1 and (b) (4) validation report CSSR-0044-02-ADD1.

Reviewer Assessment: The revisions are adequate.

- b. *In your October 31, 2022, response to our IR dated October 18, 2022, you indicated when a (b) (4) test well shows contamination on repeat testing and the sterility results on the CBU is negative, the (b) (4) assay is repeated using a post-(b) (4) sample. It is not clear which post-(b) (4) sample you are using for your repeat testing. Please describe the source of the post-(b) (4) sample used for the repeat (b) (4) assay when one of the duplicate assay (b) (4) on the post-processing sample is contaminated.*

Applicant Response

If a duplicate (b) (4) is contaminated, we will deem it a failure, i.e., the acceptance criterion has not been met. The HPC, Cord Blood will not be licensed. The following section of the SOP 14.1.015-UN have been revised: Step (b) (4) of Section 6 (b) (4) (b) (4) Section 7, Interpretation bullet point 8.

Reviewer Assessment: The response is acceptable.

- c. *Please revise the following sections of the (b) (4) SOP 14.1.015-UN (Cord Blood Hematopoietic (b) (4) Assay):*
- i. *In Section 3.0, please clarify the statement that “cord blood samples should not exceed 48 hours after collection.”*
 - ii. *In Section 4.0, you submitted a product insert for (b) (4) yet you state, (b) (4) from (b) (4) is used. Please submit the correct product insert for the (b) (4)*
 - iii. *In Section 6.0, please clarify what is being thawed for (b) (4) in ‘Step (b) (4)*
 - iv. *Please update the SOP with your response to procedures followed when an assay well is contaminated, as noted in part b above.*

Applicant Response to c.i

i. A post-processing sample is used for the (b) (4) test. This testing should be completed within 48 hours after cord blood collection. We have revised Section 2 Policies, bullet point 4 of SOP 14.1.015-UN to state that “The (b) (4) test be performed using post-processing (pre-freeze) sample within 48 hours after cord blood collection” and removed “the cord blood should not exceed 48 hours after collection” in Section 3.0

Reviewer Comment: In a follow-up information request on January 26, 2024, and response received on February 8, 2024, the Applicant explained that according to the Cord Blood BLA Guidance, Section VII. B. 10. f., you should begin processing of HPC, Cord Blood within 48 hours of collection. They decided to perform the (b) (4) assay on postprocessing (pre-cryopreservation) samples on the same day of cord blood

processing. It ensures the testing samples are still viable and possess potency. This is why SOP 14.1.015-UN states the (b) (4) test should be performed using post-processing (pre-freeze) sample within 48 hours after cord blood collection.

Reviewer Assessment: The guidance requires that cord blood processing is initiated within 48 hours of collection. The Applicant revised the SOP to perform the (b) (4) test within 48 hours of collection, which is acceptable, because it is within the same timeframe as initiation of processing from collection timepoint.

Applicant Response to c.ii

The product insert for the (b) (4) is attached to this response for review.

Reviewer Assessment: The product insert provides adequate information on the (b) (4) used for the (b) (4) assay.

Applicant Response to c.iii

The (b) (4)-based media for the (b) (4) assay is stored at (b) (4). Before use, the media (b) (4) testing. We revised Step (b) (4) of Section 6.0 Set Up of SOP 14.1.015-UN to state (b) (4) (b) (4)

Reviewer Assessment: The Applicant's response is adequate.

Applicant Response to c.iv

The procedures have been updated. Please see response to 5b for revised SOP 14.1.015-UN attached to this response.

Reviewer Assessment: The revisions to the procedures are adequate. All the responses to the (b) (4) questions are adequate.

FDA CR Comment #6

Please address the following concerns with the Thaw and Wash for RCR Process Validation report (PV-0013-01-ADD01):

- a. *Your validation report states that you are following (b) (4) sterility test methods, but you did not provide information on the test sample volume. Please provide information on the test sample volume used for this sterility testing. If you are not using test sample volume per (b) (4) please validate your method and provide a report.*
- b. *The HPC, Cord Blood test sample used for sterility testing for your thaw and wash validation may contain residual amounts of dimethyl sulfoxide (DMSO). DMSO may*

confound the results of sterility testing and mask a potential positive sterility result during your PV. If sterility test samples contain DMSO, you should provide data from bacteriostasis and fungistasis studies to demonstrate that the use of DMSO does not interfere with the detection of bacterial and fungal contaminants. The sterility test method used in the bacteriostasis and fungistasis studies should be the same method used to test your product. Please refer to the (b) (4) (b) (4) test method entitled, (b) (4) for a description of appropriate test methodology.

Summary of Applicant Response

Reference: SN0036 Response to CRL dated 20 January 2023; VQA-014, F6; VQA-014, F6

Please Note: The method suitability and sterility tests requested under CR comment #6 is for their “Thaw and Wash” process method validation study only. The method suitability and sterility test for product release testing was reviewed during the original BLA review and was found acceptable.

Reviewer Comment: The Applicant requested a Type A meeting on March 9, 2023, for clarifications on product test sample for sterility testing. This meeting request was denied as it was not appropriate as a Type A meeting. Instead, we provided a written email response to their clarification questions and held an informal telecon with the Applicant on May 5, 2023. We informed the Applicant that it was acceptable to use (b) (4) of final product (b) (4) as the sample for sterility testing. The (b) (4) (b) (4). Applicant indicates that they used the (b) (4) for the current method suitability and the sterility test for the (b) (4) process method validation study.

(b) (4) performed the quantitative method suitability test for the (b) (4) validation process. This assay is similar to the assay performed for the final product release testing. The only difference is that the Applicant sent (b) (4) for the final product sterility assay, and in this case, the (b) (4) was replaced by (b) (4) that may contain (b) (4). The Applicant used the recommended volume of the sample for this assay, and this is acceptable.

(b) (4) provided the study reports for this test that was performed per (b) (4) recommendations, and its review is summarized below:

Test Sample: (b) (4) of final product (b) (4)

Test Microorganisms: They used the following (b) (4) challenge microorganisms from (b) (4)

(b) (4) These (b) (4) microorganisms encompass aerobic and anaerobic microorganisms as well as spore formers, yeast, and fungi.

3 pages have been determined to be not releasable: (b)(4)

(b) (4)

Applicant response is acceptable.

FDA CR Comment #7

In Section 3.2.S.2.2.3, “Fresh CBU storage and transportation,” you state, “the shipping containers have been validated to maintain an internal temperature between (b) (4) for (b) (4) in both (b) (4) temperature profile extremes for both minimum and maximum loads, if packed in accordance to written procedures.” However, you did not provide the validation report conducted in both (b) (4) temperature profile extremes for the CBUs. FDA needs this report to ensure that the (b) (4) shipper maintains the internal temperature for the specified period under temperature extremes. Please provide the CBU storage and transportation validation report performed at (b) (4) temperature extremes with the (b) (4) shippers.

Summary of the Applicant’s Response

Reference: 04.1.082-PU; PQ-0054-03; PQSR-0054-03 and BLA 125764/0 SN0036 Response to BLA 125764/0 Complete Response Letter dated January 20, 2023.

- Applicant indicates that their current plan to collect donor CBUs only from (b) (4) region and the maximum transport time from collection site to the StemCyte facility is (b) (4)
- They tested the (b) (4) shipper under (b) (4) temperatures to evaluate whether the shipper was able to maintain an internal temperature of 1(b) (4) for a minimum of (b) (4)

Shipper:

- The (b) (4) is fully assembled by the manufacturer and includes 2 metal wire baskets that can hold collection materials. The shipper consists of a molded, rigid polyethylene insulation base, walls, and a lid.

Reviewer Comment: The manufacturer website indicates that the (b) (4) can hold (b) (4) of red blood cell units at (b) (4) while in transit for up to (b) (4) and the shipper was qualified by (b) (4) accredited by the American Association for Laboratory Accreditation (A2LA) to the ISO/IEC 17025 standard. However, this item has been discontinued by the supplier and is no longer available for purchase. Hence the following information request was sent to the Applicant on April 24, 2024.

Information Request to the Applicant sent on April 24, 2024: Your validated shipper for CBU transport is (b) (4) However, the manufacturer website indicates that the (b) (4) has been discontinued. Hence, we wonder whether you have enough of these shippers on hand for shipping the CBUs. Therefore, Therefore, please confirm whether you can still purchase this item from the supplier. In addition, please provide the number of validated (b) (4) shipper you have in stock and how long the currently available supply would last. Please note that if

you plan to replace this shipper with a new model in the future, you will have to validate the new shipper to confirm that it is capable of maintaining an internal temperature between (b) (4) for (b) (4) in both (b) (4) temperature profile extremes for both minimum and maximum loads, if packed in accordance to written procedures.

Applicant Response Received on April 25, 2024

We confirm that we have an adequate inventory of (b) (4) shippers. With only (b) (4) cord blood collection sites currently operating, we have (b) (4) (b) (4) shippers readily available with (b) (4) additional brand-new shippers in the warehouse for a total of (b) (4) shippers for (b) (4) collection sites. We have this surplus because of the closure of (b) (4) collection sites in 2022. Additionally, we verified with the vendor and manufacturer that (b) (4) of these shippers remain in inventory at this time should it become necessary to acquire more soon. At this time, we do not anticipate that there will be a need.

In the future, we will select a suitable model to replace the current (b) (4) shippers. We are also fully aware that validation in both (b) (4) temperature extremes to ensure an internal temperature between (b) (4) is maintained for (b) (4) as well as testing for minimum and maximum loads, will be required before using the new shipper model.

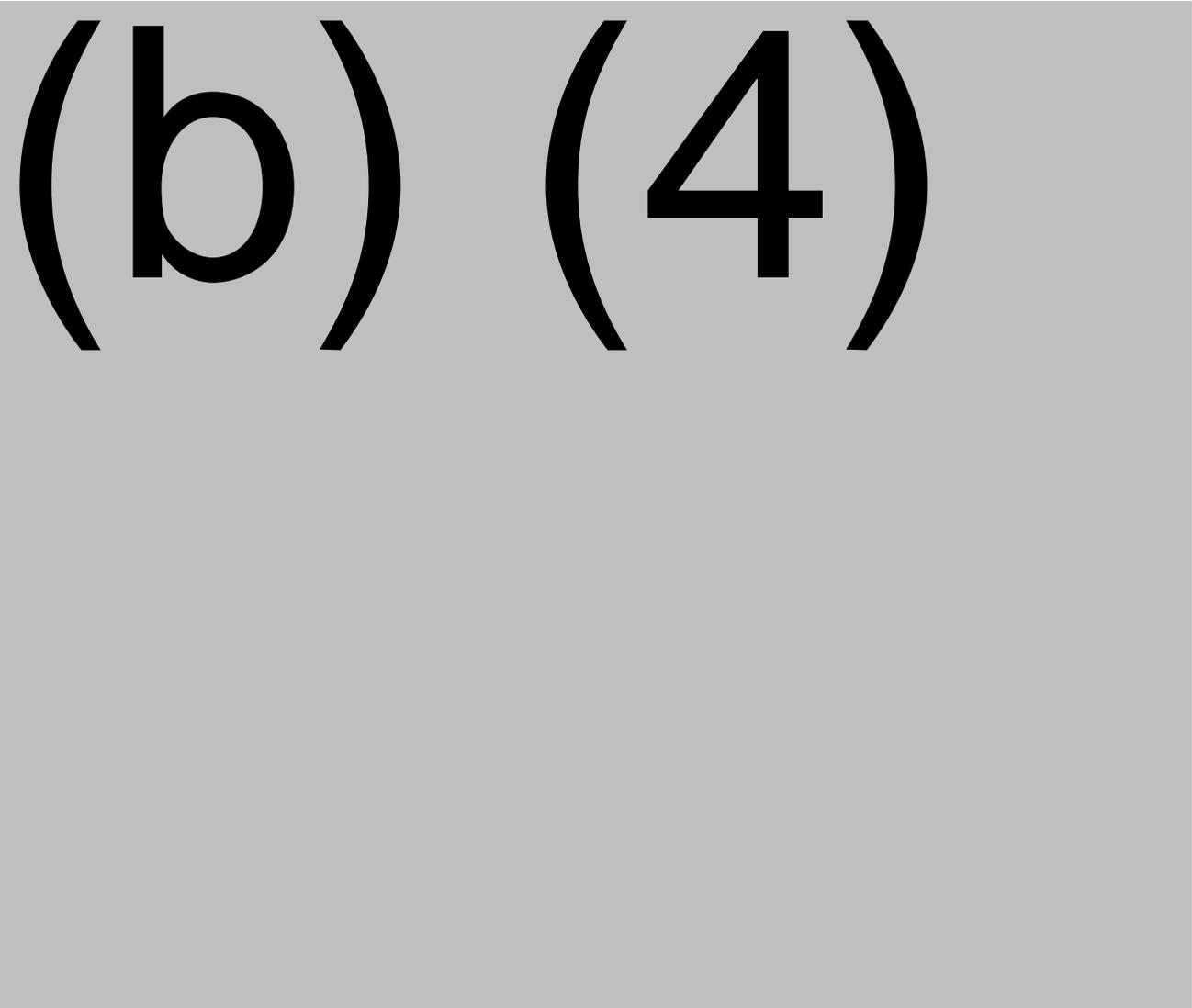
Reviewer Assessment: The Applicant response is acceptable.

Validation Procedure:

(b) (4)

1 page have been determined to be not releasable: (b)(4)

(b) (4)



Information Request Sent on January 26, 2024:

Your response to comment #7 references the following two documents PQ-0054-02 and PQSR-0054-02. However, we cannot locate these documents in your submission. Kindly confirm if these two documents were mistakenly labeled as PQ-0054-03 and PQSR-0054-03.

Applicant Response Received on January 31, 2024

Applicant indicates that PQ-0054-02 and PQSR-0054-02 available in Amendment SN0027. These documents are related to the validation of (b) (4) shipper at (b) (4) for (b) (4) PQ-0054-03 and PQSR-0054-03 demonstrate that the (b) (4) shipper was validated under (b) (4) extremes.

Reviewer Assessment: The Applicant's response is acceptable.

Information Request Sent on January 26, 2024:

The footer section of Validation ID: PQ-0054-03 states, "Effective Date: 3/11/2016 Revision: 2 01.3.007-08-UN" and the footer section of PQSR-0054-03 states, Effective Date: 10/12/2015 Revision: 2 01.3.007-10-UN. Please clarify the meaning of the information in the footer sections in these SOPs and the rest of all the SOPs in your submission

Summary of Applicant Response Received on January 31, 2024

- Document control numbers (footnotes) are not to be confused with Validation ID numbers, which appear in the upper right corner of the validation documents.
- The 01.3.007-08-UN (R2, Effective Date 3/11/2016) is the Performance Qualification Template for equipment PQ.
- The 01.3.007-10-UN (R2, Effective Date 10/12/2015) is IQ, OQ, PQ, or IOPQ Qualification or Validation Summary Report Template to document IOPQ outcomes.
- Both are controlled documents.

Reviewer Assessment: The Applicant's response is acceptable.

FDA CR Comment #8

In SOP 13.1.026-PU, "Cord Blood Unit Sample Receipt and Accessioning," you state, "if the CBUs does not meet the pre-processing acceptance criteria, the lab manager or the CBB Medical Director will make the final decision on whether the cord blood unit should remain stored or discarded." You did not provide any details about the criteria the lab supervisors will use to determine if CBUs not meeting the pre-processing specification should be processed. In addition, you did not clearly indicate the pre-processing acceptance criteria for fresh CBUs. Therefore, we cannot determine whether your pre-processing acceptance criteria are adequate. Please address the following:

- a. *Please explain the criteria that will be used by the supervisor or lab manager or Cord Blood Bank (CBB) medical director to allow the use or discard the pre-processed CBU with appropriate justification.*
- b. *Please provide a table of parameters with acceptance criteria for pre-processed CBUs.*

Summary of Applicant Response

Reference: BLA 125764/0 SN0036 Response to BLA 125764/0 Complete Response Letter dated January 20, 2023; SOP 13.1.026-PU

- Applicant indicates that they have developed several triaging and accessioning procedures to examine the CBUs received at the manufacturing facility before

processing them to generate the drug product. That includes, verification of (b) (4)

- The acceptance criteria for accepting the CBU is provided in Table 11, and also included in SOP 13.1.026-PU in section 7.

Table 11: The acceptance criteria for accepting the CBU starting material

(b) (4)

- The reason for evaluating the pre-Processing (b) (4) is that the transplant centers are requesting HPC, Cord Blood with (b) (4) (over (b) (4) (b) (4) especially for adult patients.
- If a CBU is found leaking, a Lab Supervisor or Designee is informed immediately and the CBU is discarded. The status is documented by taking photos and filing them in the corresponding pre-labeled manila folder. The status of the CBU is also recorded in Section 1 of the Public Cord Blood Processing Worksheet pg. 1 (13.3.002-01-PU).

Reviewer Assessment: The Applicant has provided a table with acceptance criteria for pre-processed CBUs. If the CBUs do not meet the criteria as indicated in above table, the supervisor or lab manager or Cord Blood Bank (CBB) medical director may make the decision to discard the pre-processed CBU. The Applicant's response is acceptable.

FDA CR Comment #9

In SOP 14.1.039-PU, you indicate that the Medical Director reviews (b) (4) test results with (b) (4). While it appears that the Medical Director decides on whether these units are used, the basis used to make decisions on these units and the procedures you follow regarding the dispositions of these units are not clear. Therefore, please describe how CBUs with (b) (4) are handled and discuss the decision-making process to dispose of these units. Also based on this statement, it appears you have an in-process criteria for (b) (4) as a control for your manufacturing, but you did not describe in-process criteria. Please describe these criteria.

Summary of Applicant Response

Reference: BLA 125764/0 SN0036 Response to BLA 125764/0 Complete Response Letter dated January 20, 2023; SOP 14.1.039-PU (b) (4) for Public Donated Cord Blood; Form 13.3.001-02-PU (b) (4) RCR Individual Processing Log – Public Bank; Form 16.3.007-01-PU QA Batch Release Review and Cord Source Data Entry Verification; 16.3.002-10-UN Disposition/Discard Form.

- The acceptable pre-processing (b) (4) and post-processing TNC Count: $\geq 90 \times 10^7$.
- The in-process criteria for (b) (4)
- If (b) (4) in the pre-processing sample is observed, QA personnel will notify Medical Director for review.
- These (b) (4) will be marked on Form 13.3.001-02-PU, (b) (4) RCR Individual Processing Log-Public Bank and Form 16.3.007-01-PU QA Batch Release Review and Cord Source Data Entry.
- In the meantime, the lab personnel will continue processing the CBU unit to generate HPC-Cord Blood product.
- QA will forward donor's batch record to Medical Director for further review of the donor's health status and the (b) (4)
- If Medical Director review of the donor records and (b) (4) (b) (4) is a risk to the CBU, the processed CBU will be discarded.
- The details about discarding the product will be documented in Form 16.3.002-10-UN used to record CBU Disposition/Discard

Reviewer Assessment: The Applicant provided the in-process criteria for the limits of (b) (4). The manufacturing team records the (b) (4) in appropriate forms for documentation and reference. Medical director reviews the donor medical history and the CBUs with (b) (4) (b) (4) (b) (4) and decides whether to allow the processed HPC-Cord Blood for distribution. However, they did not specify the basis for the Medical Director to make the decision to allow the use of HPC-Cord Blood. We sent the below IR for further clarification, and since this fall under clinical practice the clinical reviewer was engaged in the review of the IR response. Otherwise, the Applicant's response is acceptable from the CMC perspective.

Information Request Sent on January 26, 2024: *In response to the complete response comment #9, requesting for the criteria the medical director uses to decide whether to utilize or reject the HPC, Cord Blood, you mentioned that the Medical Director assesses the donor medical history and decide. Could you please specify which details in the donor medical history guide the medical director in deciding whether to accept or reject the HPC, Cord Blood unit? Please provide a list of unacceptable medical conditions of the donor that will cause rejection of the HPC, Cord Blood unit.*

Summary of Applicant Response Received on February 8, 2024

The applicant has listed the following unacceptable medical conditions under which the medical director will reject the donor HPC, Cord Blood for distribution purpose.

(b) (4)

Reviewer Comment: On February 13, 2024, I requested the clinical reviewer Dr. Prateek Shukla to review the Applicant response for sufficiency and his response was follows: “I have looked at these responses and these are acceptable. These risks are also already included in the labeling under potential adverse events. The product class relies primarily on history of the mother at the time of cord blood collection as often, the baby has not had enough time to develop much of a history. These are still important considerations but are not routinely collected at time of collection. I am glad that they have considered these potentials and that they are included in the labeling.”

Reviewer Assessment: Based on the review of Applicant’s response by the clinical reviewer, we accept the Applicant’s response.

FDA CR Comment #10:

For the stability program for HPC, Cord Blood product, you have not provided appropriate documents that describe which protocol would be followed to establish a longer product expiration. Furthermore, it is not clear which protocol was executed to generate the submitted stability data. Please address the following:

- a. *Please submit a stability protocol that describes how you executed the stability study in support of the expiration date.*

Applicant Response

Reference: CSR-0088-01

A stability protocol, CSR-0088-01, is submitted.

Description of the stability study executed: The study was executed on July 7, 2023, using HPC, Cord Blood units banked in (b) (4) (b) (4) of the oldest cryopreserved HPC, Cord Blood units (banked in (b) (4)) manufactured by (b) (4) processing were used for the stability study. The units were thawed at 37°C water bath for 5 minutes, then diluted with (b) (4) of wash buffer (b) (4) human serum albumin in Dextran 40 in 0.9% NaCl) and washed by centrifugation (b) (4) g for 20 minutes at 2- 8°C). The cell pellet was (b) (4) of SOP 14.1.031-01-PU (Tests for Cryopreserved CBU in the Stability Program). Samples of the washed cells were taken and analyzed for TNC, cell viability, viable CD34+ cells, (b) (4) and sterility

(sterility samples is composed of (b) (4) in accordance with their applicable SOPs. Table 12 lists the revised pre-specified acceptance criteria to meet.

Table 12: Revised Pre-specified Acceptance Criteria

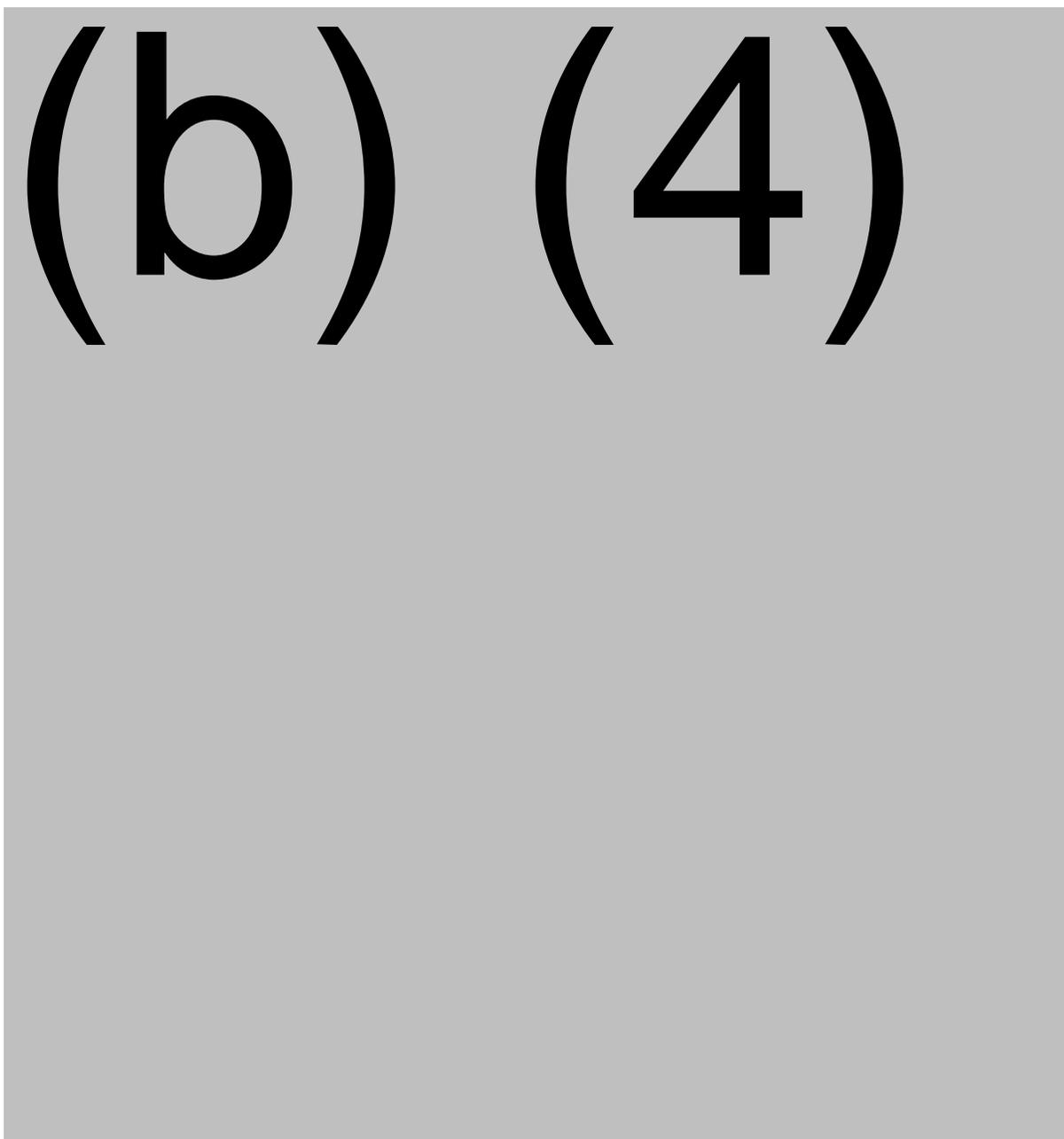


Reviewer Assessment: In a February 8, 2024, response to our follow-up information request on January 26, 2024, StemCyte revised the (b) (4) criterion to (b) (4) from (b) (4). The stability protocol document CSR-0088-01 has been updated accordingly. The revision is acceptable.

Based on the stability study results the expiration of the HPC, Cord Blood is established at 12 years or 14 months.

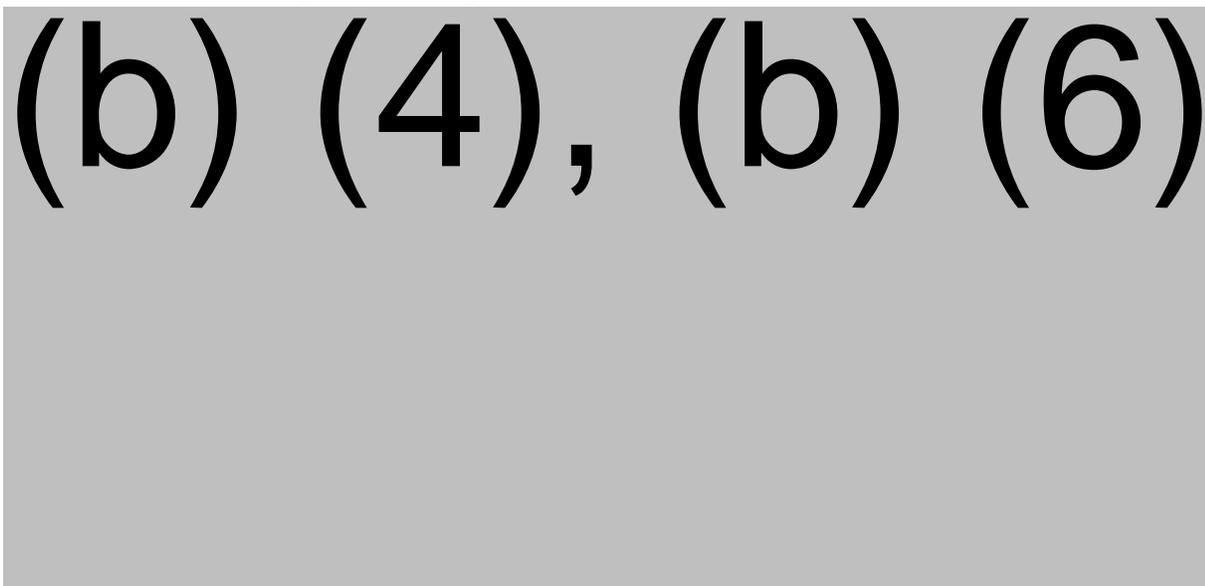
The stability study protocol is presented in the flow chart in Figure 6.

Figure 6: CBU Stability Flow Chart



Reviewer Comment: The (b) (4) specification in the flow chart has been updated to (b) (4) in a February 8, 2024, response to a follow-up information request on January 26, 2024.

Table 13: Summary of Stability Studies



Reviewer Assessment: The stability study and results are adequate. Based on this data, the HPC, Cord Blood expiration can be established at 12 years or 144 months.

- b. Please submit a stability study report in support of the expiration date. The report should include a summary of the results obtained and any deviations and explanation/discussions of the results.*

Applicant Response

Reference: CSSR-0088-01

A stability study report CSSR-0088-01 is submitted. (The summary of the stability study and results have been documented in the response to 10a). The summary is the same as in Table 13.

Reviewer Assessment: The stability study results are adequate to establish a product expiry of 12 years or 144 months (2011-2023).

- c. Please submit a stability protocol that will be executed yearly to establish longer product expiration. The protocol should specify the number of units that will be thawed, the pre-specified criteria to meet, and how the study will be conducted. Please be advised that you will need an approved stability protocol in the BLA that will be executed annually to advance the expiry of the HPC, Cord Blood product.*

Applicant Response

Reference: SOP 01.1.027-01-PU; 32p81; 32p82; 32p83

Document number 01.1.027.1-PU describes StemCyte Stability Program that will be executed annually to advance the expiration of the HPC, Cord Blood product.

As described in 10a, a minimum of (b) (4) of the oldest HPC, Cord Blood units in storage will be (b) (4) selected, thawed, washed, and analyzed to meet established criteria as described in the response to 10a.

Reviewer Assessment: This response is adequate.

- d. *In the stability protocol and report, please refer to the appropriate SOP (number and title) that describes the assays you perform rather than duplicating the same SOP.*

Applicant Response

Reference: SOP 14.1.040-PU, SOP 14.1.039-PU, SOP 14.1.023-UN, and SOP 14.1.015-UN

This was done. (See response to 10a)

Reviewer Assessment: This comment has been adequately addressed. The Applicant referred to SOPs that were being followed. See flow chat in response to 10a above.

- e. *In your table titled, “2022 CBU Stability Summary for RCR units,” in support of expiration dating of your HPC, Cord Blood product, you provided two entries for “Post-thaw (b) (4)” and “Post thaw (b) (4).” The results entered for the first set of ‘Post thaw (b) (4)’ and ‘Post thaw (b) (4)’ are entered as N/A without any explanation. Please clarify these entries for (b) (4) and the ‘post-thaw’ results in support of your HPC, Cord Blood product stability.*

Applicant Response

Reference: 2022 CBU Stability Summary for RCR units

It was a mistake to use “post-thaw” to describe the (b) (4) testing for post-processing (pre-freeze) sample. The stability study has been repeated and the data resubmitted in the Nov 23 response to CR comments.

Reviewer Assessment: The stability data has been submitted. The Applicant recognized the error with the previous data. The response is adequate.

FDA CR Comment #11

In SOP 16.1.002-UN, you indicate that you retain a maximum of (b) (4) of umbilical cord tissue as retention samples. However, umbilical cord tissue alone is not a representative of each HPC, Cord Blood. As outlined in 21 CFR 211.170(b)(1), an

appropriately identified reserve sample that is representative of each lot or batch of drug product shall be retained and stored under conditions consistent with product labeling. In addition to the umbilical cord tissue, you should retain other samples that are appropriately identified and representative of HPC, Cord Blood. Therefore, please provide a plan for retaining product samples that are appropriately representative of HPC, Cord Blood. Please note that these samples must be retained and stored at temperatures and under conditions that will maintain their identity and integrity and are consistent with product labeling for one year after the expiration of the HPC, Cord Blood.

Summary of Applicant's Response

Reference: BLA 125764/0 SN0036 Response to BLA 125764/0 Complete Response Letter dated January 20, 2023, and SOP 16.1.002-01-PU Storage of Cryopreserved HPC, Cord Blood

SOP 16.1.002-01-PU provides procedure for retaining representative samples for HPC-Cord Blood. They will prepare (b) (4) segments with ISBT label on each and they are directly attached to the cryobag. (b) (4) of will be retained in the same liquid nitrogen storage container after the distribution of HPC-Cord Blood. In addition, (b) (4) (b) (4) of Umbilical Cord Tissue (UCT) are also part of the retention samples.

Reviewer Assessment: The Applicant provided their plan for the retention samples. The information provided by the Applicant and in the SOP 16.1.002-01-PU are acceptable.

FDA CR Comment #12

In SOP 17.1.005-UN, "Thaw and Wash for Red Cell reduced (RCR) Units," you indicate that the final product is stored in a refrigerator at 2° C to 8° C until transplantation and the infusion time should not exceed 2 hours post-thaw. However, you did not submit data to support the holding temperature of 2°C to 8°C for a maximum of 2 hours. To support the proposed holding conditions, you should provide validated data for holding temperature and time. An expiration time should be based on this validation study that accounts for the maximum time for infusion. Your thaw and wash validation report should support the conditions you describe (i.e., holding the HPC, Cord Blood at 2°C to 8°C until transplantation). Please submit the thaw and wash validation report to support the holding temperature and time.

Summary of Applicant's Response

Reference: BLA 125764/0 SN0036 Response to BLA 125764/0 Complete Response Letter dated January 20, 2023, and SOP 17.1.005-UN (2.0 Policies, bullet point 5); In-Use Stability (b) (4) RCR HPC, Cord Blood Characterization Study (CSR-0082-03 and CSSR-0082-03).

The CSR-0082-03 report provides information about the procedure used for the stability testing of thawed HPC-Cord Blood. The procedure indicates that they thawed CBUs and hold them at 2-8°C, washed them after 0, 1, 2 and (b) (4) hours post thaw, and

evaluated the product for cell viability by (b) (4) assay (SOP 14.1.040-PU), (b) (4) CD34 enumeration (SOP 14.1.023-UN), and (b) (4) Assay (SOP 14.1.015-UN).

Reviewer Comment: Based on the narrative provided in the Applicant's response, it appears they tested the thaw and hold cells instead of testing the thaw, wash, and hold cells. I had a discussion with Dr. Mercy Quagraine on January 12, 2024, and she confirmed that they must perform this test on thaw, and wash cells. In addition, she recommends that cell viability test by (b) (4) alone is sufficient to evaluate the cells at different time points. This was resolved via IR.

Information Request Sent on January 26, 2024: In response to comment #12 regarding your process validation, you indicate that you thawed CBUs, and (b) (4) (b) (4) you hold at 2°C to 8°C and sample at 0-, 1-, 2-, and (b) (4) hour time points for viability, CD34, and (b) (4) assays. Please note that according to the Cord Blood BLA guidance, section V.D.2, the HPC, Cord Blood units used for validation should be washed to remove cryoprotectant. The time dependent study that you conduct should be used to establish the time limits within which the thawed and washed HPC, Cord Blood unit is infused into patient. Please submit validation data with washed HPC, Cord Blood units which establish holding conditions for the thawed and washed HPC, Cord Blood unit. This should include the holding temperature and the time duration held at this temperature before transplanted into patient.

Applicant Response to Information Request Received on February 8, 2024

The (b) (4) frozen CBUs were thawed and washed based on SOP 17.1.005-UN, Thaw and Wash for Red Cell Reduced (RCR) units. Section 6.4 of SOP 17.1.005-UN describes the thawing and washing procedures for processing cryopreserved CBUs. 6.1 Test Description on page 5 of the CSR-0082-03 indicates that this test will track viability of thawed and washed (b) (4) RCR CBUs at 2-8°C at 0, 1, 2, and (b) (4) hours. In the characterization study, we referred to thawed RCR units as thawed and washed RCR units. The viability of CD34 and TNC and (b) (4) assay results were obtained from thawed and washed CBU samples stored at 2-8°C at 0, 1, 2, and (b) (4) hours. We apologize for any confusion caused by the term “thawed RCR units” used in the protocol and report as it was not specific enough to indicate that washing was also performed. We revised the language in characterization study and summary report to include “thaw” and “wash” to clarify and confirm that both thawing and washing procedures were followed during the execution of this study. Please see amended section 1, 2, and 6.2 of CSR-0082-03-amended and amended section 1.1, 1.2, 3, and 4 of CSSR-0082-03-amended.

Reviewer Assessment: Applicant states that the (b) (4) frozen CBUs were thawed and washed based on SOP 17.1.005-UN, Thaw and Wash for Red Cell Reduced (RCR) units. They indicate that the SOPs refer to “thawed and washed” as “thawed,” and they have performed the study on thawed and washed cells. They have changed the term “thawed” to “thawed and washed” in CSR-0082-03, In-use Stability for (b) (4) RCR HPC Cord Blood Characterization Study and CSSR-0082-03 Refrigerated In-use stability for (b) (4) RCR HPC Cord Characterization Study Report. The Applicant's response is acceptable. The review of these reports follows.

Review of Applicant’s Response to Comment #12

- CSR-0082-03, In-use Stability for (b) (4) RCR HPC Cord Blood Characterization Study provides protocol for the validation of the stability of thaw, wash and hold cells. The study was designed to evaluate the stability of the cells at different hold times after thaw and wash.

Procedure: (b) (4)

[Redacted]

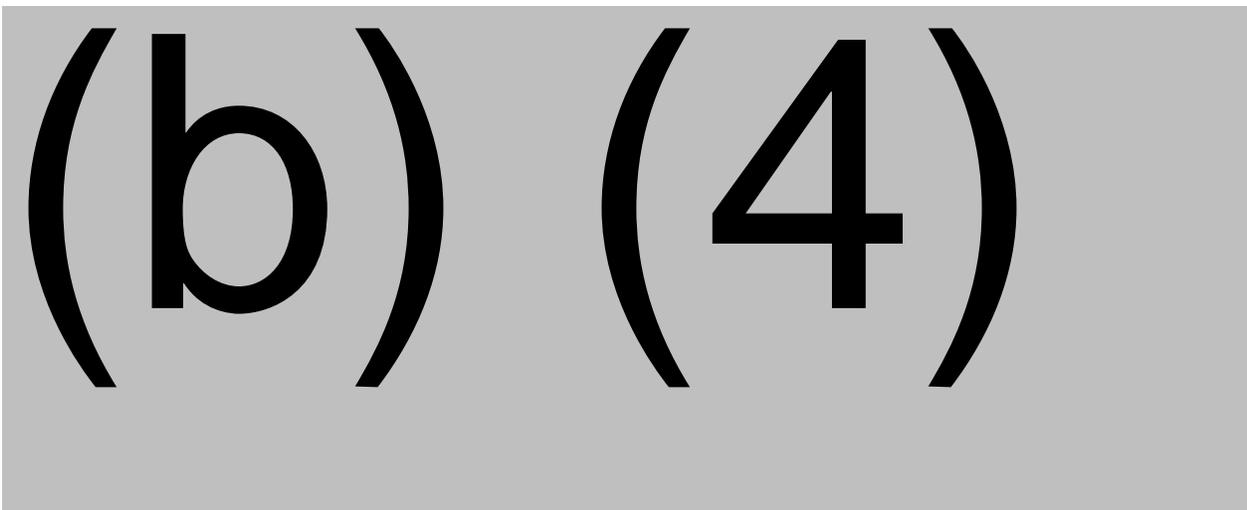
(b) (4)

- The applicant has provided the results for the analysis in CSSR-0082-03-amended document. The review of their results confirms that the cell viability and CD34 positive cell viability remained above (b) (4) in all the (b) (4) samples tested and at all time points. One of the (b) (4) samples tested is shown here for representation.

CBU (b) (4), (b) (6)	Banked Date	Thaw Date	Cell Viability (%)	CD34 Viability (%)
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(b) (4)

- The (b) (4) counts were greater than (b) (4) at all the (b) (4) tested time points for all the (b) (4) HPC, Cord Blood.



The analysis of HPC, Cord Blood up to (b) (4) hours hold at (b) (4) after thaw and wash indicate that they pass the acceptance criteria.

Reviewer Assessment: The thaw and wash validation report for HPC, Cord Blood was performed at 2°C to 8°C until transplantation. The Applicant has provided data to support the holding temperature of 2°C to 8°C for a maximum of 2 hours. An expiration time was derived based on this validation study. The Applicant’s response is acceptable.

FDA CR Comment #13

In your SOP 14.1.027-UN for “HLA Sample Preparation and Shipping to (b) (4)” you include ‘oral swabs’ as samples for HLA-typing and include (b) (4) as a supply used in the assay. As described in our cord blood licensure guidance (<https://www.fda.gov/media/86387/download>), ‘oral swabs’ is not an appropriate sample for HLA-typing. HLA-typing should be performed on cord blood from attached segments of HPC, Cord Blood. In addition, there is no step/section in the SOP describing how the (b) (4) is used. Please revise your SOP to be consistent with our cord blood licensure guidance and clarify the purpose of the (b) (4)

Applicant Response

SOP 14.1.027-UN has been revised to remove (b) (4) and ‘oral swabs’ in Section 6.2 Step (b) (4). The samples for HLA-typing are (b) (4) cord blood for initial HLA typing and an attached segment of the HPC, Cord Blood for confirmatory HLA-typing in Section 6.1 Step (b) (4) of the SOP. The revised SOP 14.1.027-UN is submitted for review.

Reviewer Assessment: The response is adequate. The revisions to SOP 14.1.027-UN are acceptable.

FDA CR Comment #14

You mention that for confirmatory HLA-typing at (b) (4) stored samples will be used and that sample preparation for shipping to (b) (4) follow SOP 14.1.012-UN (Shipping of Samples for confirmatory HLA Typing). Please address the following:

- a. Please be aware that Confirmatory HLA typing should be done on contiguously attached segment and not on stored samples. Please revise your sampling strategy and SOP accordingly.*

Applicant Response

Reference: SOP 14.1.012-01-PU

SOP 14.1.012-01-PU was created to describe the shipment of samples of HPC, Cord Blood for confirmatory HLA-typing. The sample requirement for confirmatory HLA typing is defined in Section 3.0 (Sample Requirements) and Section 6.1.1 of the SOP. The attached segment of the HPC, Cord Blood will be used for confirmatory HLA-typing.

Reviewer Assessment: The applicant's response is adequate. Only a contiguously attached segment may be used for the confirmatory HLA-typing (confirmatory, to confirm the initial HLA-type).

- b. You did not submit this SOP. Please submit SOP 14.1.012-UN Shipping of Samples for confirmatory HLA-Typing.*

Applicant Response

The SOP 14.1.012-UN is replaced by SOP 14.1.012-01-PU which is submitted for review.

Reviewer Assessment: The response is adequate. This SOP describes how contiguously attached segment (cryopreserved) samples are shipped for confirmatory HLA-Typing.

FDA CR Comment #15

In Section 3.2.P.3.3, Table 1, you did not include CD34+ cell count in the HPC, Cord Blood Unit Release Specifications. As described in our cord blood guidance licensure guidance CD34+ cell count is a critical parameter for the quality of HPC, Cord Blood. Therefore, please include total CD34+ cell count as part of HPC, Cord Blood unit release specification and revise Table 1 in Section 3.2.P.3.3 accordingly.

Summary of Applicant's Response

Reference: BLA 125764/0 SN0036 Response to BLA 125764/0 Complete Response Letter dated January 20, 2023, and Section 3.2.P.3.3.

The Applicant has updated the Table to include CD34+ cell count in the HPC, Cord Blood Unit Release Specifications. The updated Table 15 is shown below.

Table 15: HPC, Cord Blood Unit Release Specifications

Parameter	Specification	Sampling and Method
TNC count	≥ 90 x10 ⁷	(b) (4)
Viable TNC	≥ 85%	
Viable total CD34+ cells	≥ 1.25 x10 ⁶	
Microbial testing (Sterility)	No detectable microbial growth	
(b) (4) assay (b) (4)	(b) (4)	
Donor screening and infectious disease testing	Donor meets criteria defined in CFR 1271, Subpart C. All infectious disease markers are tested non- reactive/negative. CMV results are recorded.	
Human leukocyte antigen (HLA) typing	Report	
Confirmatory HLA typing	Confirms initial typing	
ABO/Rh type	Report	
Hemoglobin Testing	No homozygous or double heterozygous for hemoglobinopathy	

Reviewer Assessment: The Applicant's response is acceptable.

FDA CR Comment #16

For the CD34+ flow cytometry assay used as a part of product release, (b) (4) package insert for CD34 Enumeration Kit recommends (b) (4) (b) (4). However, in SOP 14.1.023-UN, revision 2, Section 6.13, you are proposing to (b) (4). It is not clear whether deviating from the suggested package insert (b) (4) will affect the accuracy of your enumeration. Please provide a justification for choosing (b) (4) threshold for (b) (4) the CBU and not using (b) (4) recommended threshold for (b) (4).

Applicant response

Reference: SOP 14.1.023-UN

The SOP 14.1.023-UN was revised to add (b) (4) (b) (4) in Section 6.1 Sample Preparation, (b) (4) to meet (b) (4) CD34 Enumeration Kit instruction. The revised SOP 14.1.023-UN is attached to this response for review.”

Reviewer Assessment: Revised SOP 14.1.023-UN indicates that they will (b) (4) the CBU according to (b) (4) CD34 Enumeration Kit instructions. In response received on March 19, 2024, to an IR dated March 13, 2024, the Applicant has further clarified that the updated validation study CSR-0083-03 and CSSR-0083-03 described the (b) (4) according to (b) (4) instructions. This is acceptable.

FDA CR Comment #17

With reference to CSR 0083-02 submitted on October 21, 2022 (SN0025), in response to our IR dated July 27, 2022, you performed (b) (4) with expected outcomes of (b) (4) respectively. However, it is unclear why you performed (b) (4). If the purpose of this study is to find the limit of detection, then you should (b) (4) until you are able to achieve the limit of detection. Please provide a justification for your (b) (4) and provide data to determine the lower limit of detection.

Applicant response

Reference: CSR-0083-03, CSSR-0083-03, 13.3.002-01-PU; 13.3.001-01-UN, (b) (4) (b) (4)

The CSR-0083-02 and CSSR-0083-02 were performed for linearity of CD34 counts at (b) (4) but not for the limit of detection. We repeated the detection of CD34 counts using the (b) (4) stem cell enumeration kit on post-processing and post-thaw CBU samples based on SOP 14.1.023-UN.

(b) (4) CD34 Enumeration (b) (4) ”. The linear regression and obtained at least (b) (4) viable (b) (4) events at each run (Section 6.7 Step #3) are used to analyze the test results to determine maximal (b) (4) for the test samples with (b) (4) (b) (4) and the limit of detection based on the (b) (4) detection using flow cytometry is recommended by (b) (4)

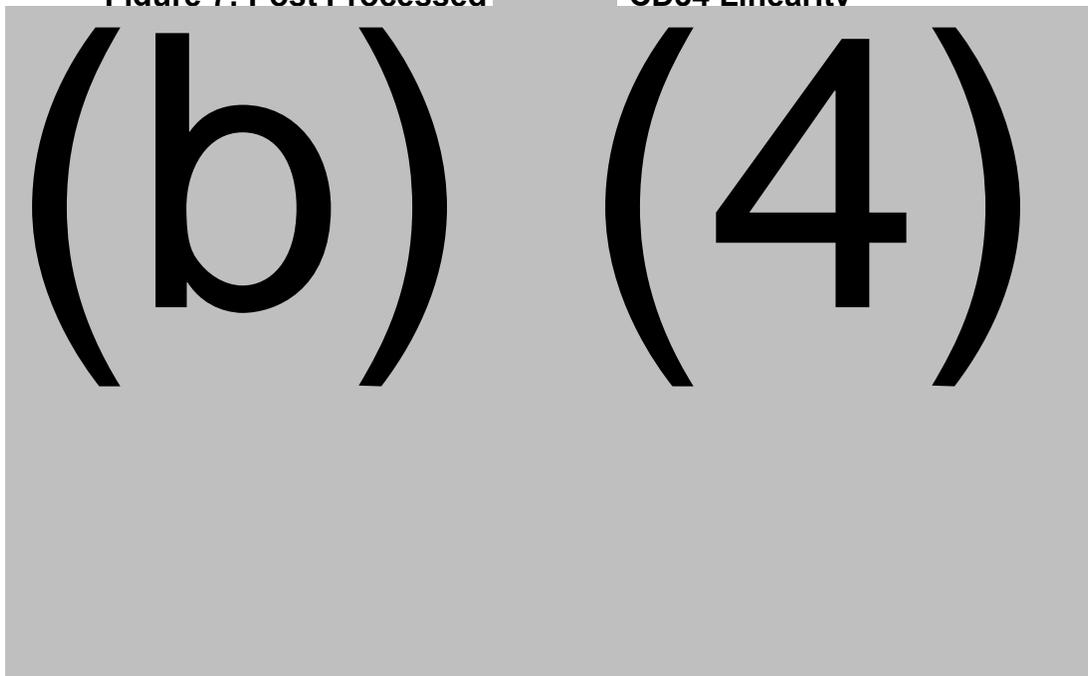
The CSR-0083-03 and CSSR-0083-03 are attached to this response for review”.

Reviewer Assessment: In an IR dated July 27, 2022, we questioned the rationale of the (b) (4) study performed (CSR 0083-02 submitted on October 21, 2022, SN0025), where data for (b) (4) with expected outcomes of (b) (4) (b) (4) respectively, was presented. If the purpose of the study was to determine lower limit of detection, then more (b) (4) should have been tested.

The Applicant clarified that (b) (4) studies shown in CSR-0083-02 and CSSR 0083-02 submitted on October 21, 2022, were not for the purpose of limit of detection but to show linearity of CD34+ counts. However, the Applicant performed new studies to determine lower limit of detection for post processed and post thaw cord blood units and submitted this data in CSR-0083-03 and CSSR-0083-03 in their resubmission dated November 9, 2023. (b) (4) post processed and (b) (4) post thaw CBU were tested for limit of detection for viable CD34+ cells/ uL. CBUs were (b) (4) (b) (4) and tested for CD34 enumeration in (b) (4) Absolute CD34 counts were (b) (4)

Linear regression analysis was used to analyze the test results at different concentrations. All the CBU samples met the acceptance criteria of $R^2 > (b) (4)$ This data shows that the Applicant can successfully enumerate CD34+ cells at lower levels. The graph, below, shows expected vs. measured CD34 cells with $R^2 = (b) (4)$

Figure 7: Post Processed (b) (4), (b) (6) CD34 Linearity



FDA CR Comment #18

In section 3.2.S.4.1, Table 1, you indicate that donors meet criteria defined in “CFR 1270.21.” However, for human cells, tissues, or cellular or tissue-based products (HCT/Ps) recovered (collected) after May 25, 2005, a donor eligibility determination must be made, as specified in 21 CFR 1271 Subpart C. Therefore, please revise this table accordingly and submit the revised table.

Summary of Applicant Response

Reference: 3.2.S.4.1

The donor eligibility determination in Table 1 of section 3.2.S.4.1 was revised to specify in 21 CFR 1271 Subpart C. The TNC count was changed to 90x10e7. Please see revised 3.2.S.4.1 attached to this response. The changes are highlighted yellow.

Reviewer Assessment: The Applicant has revised Table 1 in section 3.2.S.4.1 per the request. Their response is acceptable.

FDA CR Comment #19

You requested categorical exclusion for environmental assessment under 21 CFR 25.31(j). However, your product is not classified under transfusable human blood or blood components and plasma. Therefore, please provide a request for categorical exclusion under 21 CFR 25.31(c) for marketing approval by revising this section in your submission.

Summary of Applicant’s Response

Reference: BLA 125764/0 SN0036 Response to BLA 125764/0 Complete Response Letter dated January 20, 2023, and section 1.12.14.

Reviewer Assessment: The Applicant requested categorical exclusion under 21 CFR 25.31(c) for marketing approval. The response is acceptable.

FDA CR Comment #20 - 23

We performed pre-license inspection (PLI) of the Baldwin Park, CA facility from August 29 to September 2, 2022, during the original BLA review. DMPQ decided not to inspect the facility again as the Applicant’s response to FDA CR comments 20 - 23 provided by DMPQ were acceptable. Please see attached concurred DMPQ review memo for details related to Applicant response to comments 20 - 23.

FDA CR Comment #24 (LABELING)

We reserve comment on the proposed labeling until the application is otherwise acceptable. We may have comments when we see the proposed final labeling.

Reviewer Comment:

In-Process Labeling

The review of in-process labeling sections was completed in the original BLA review and was acceptable.

Full Prescribing Information

Prescribing information (PI) was reviewed and revisions were made to the draft the Applicant provided in the original BLA submission and the updated instructions for preparation for infusion section provided on April 5, 2024. The revised PI was interactively reviewed with the Applicant and all the comments were resolved in 125764/0.49 submitted by the Applicant on October 18, 2024.

Container and Package Label

The final product label is reviewed under this section. The Applicant submitted a Tie Tag Label containing 4 quadrants, and a Cord Blood Cryobag Label and Small Bar Code Label with Unique Identifier. We noticed errors in the Tie Tag Label and had an informal telecon with the Applicant on April 1, 2024, to explain the errors and sent an IR on April 2, 2024, formally requesting the Applicant to address the following issues in the Label.

- Move the “For Use by Intended Recipient Only from quadrant 3 to quadrant 2.”
- Move the “Rx Only” from quadrant 3 to quadrant 1.
- Include Hydroxyethyl starch in quadrant 2.
- Include the missing degree (°) symbol in “Store at -150°C.”
- Include Label version in Quadrant 4.
- Include US License #

The Applicant responded on April 5, 2024, indicating that they have used ISBT 128 (b) (4) program designed and implemented in accordance with ICCBBA Standards to generate the Tie Tag Label. They state that the software can achieve all the label format requests that FDA made with the exception of the degree symbol and justify that per US Consensus Guidance (pp. 115-116, Section 9.4.2 Licensed Cord Blood Products) the degree (°) symbol is not required in the Label. We requested APLB for the review of Applicant’s response.

APLB responded to our request on April 11, 2024, and provided a link to the US Consensus Standard and highlighted the following: “Provided that small fonts are used, there is usually sufficient space to avoid abbreviation of any label or additional text with the exception of common abbreviations such as mL for milliliter(s) and C for degrees Celsius (Centigrade). Should abbreviations be absolutely necessary, they should conform to those listed in the Appendix.” The Appendix of the standard document recommends using C for degree Celsius (centigrade). The Applicant response related to (°) symbol and the submitted example labels as shown below are acceptable.

The Applicant submitted the updated Tie Tag Label on October 18, 2024. They included the proprietary name REGENECYTE in the label.

Figure 8: Example Tie Tag Label

 (b) (4), (b) (6)	 O Rh POSITIVE
Collection Date/Time (b) (4), (b) (6)	For Use by Intended Recipient(s) Only For Intravenous Administration Unrelated Donor See package insert for full prescribing information and instructions for preparation.
Do Not Irradiate Do Not Use Leukoreduction Filter RX Only	 Expiration Date/Time (b) (4), (b) (6)
 (b) (4), (b) (6) DESIGNATED HPC, Cora Blood (REGENECYTE) 10% DMSO, 1% DEXTRAN 40, 1% Hydroxyethyl starch, Buffy Coat Enriched, Cryopreserved, Red Cell Reduction	Intended Recipient: SAMPLE, SAMPLE Recipient ID: (b) (4), (b) (6) Date of Birth: (b) (4), (b) (6) Stemcyte, Inc. 13800 Live Oak Avenue, Baldwin Park, CA 91706 L168.001
Approx _____ mL Store at -150 C or colder US License #: XXX	

Figure 9: Example Cord Blood Cryobag Label and Small Bar Code Label with Unique Identifier

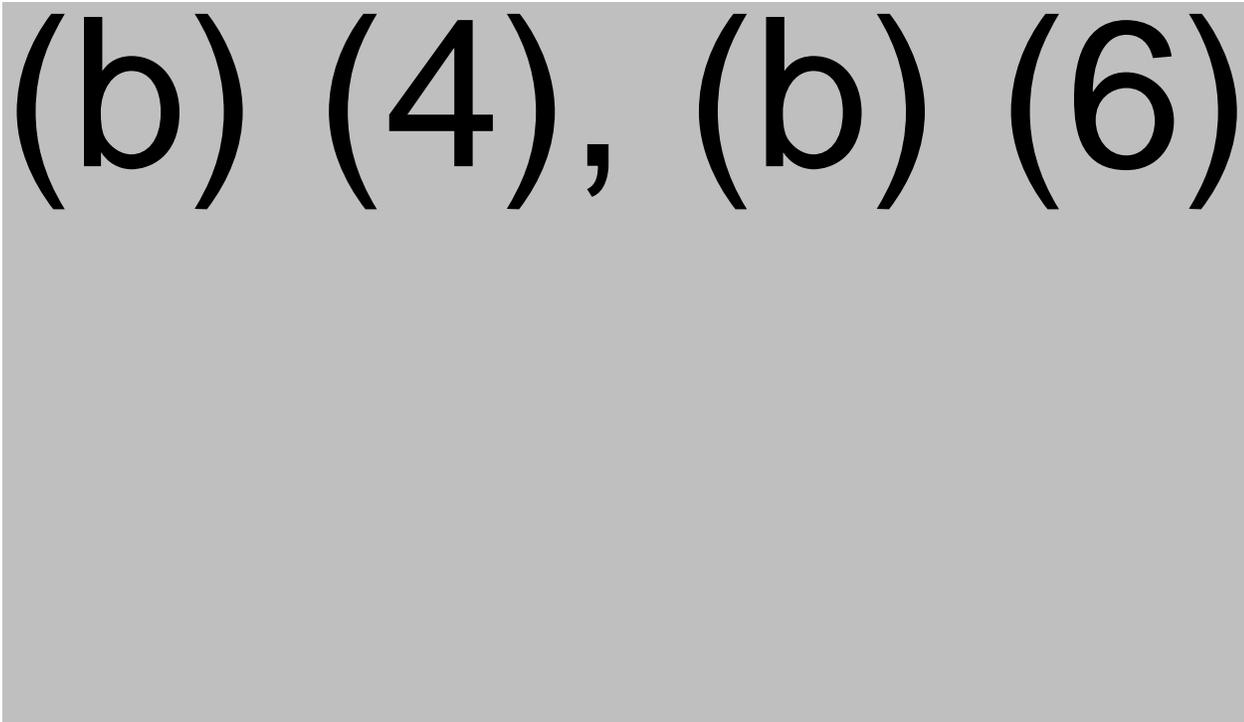


Figure 10: Example of Tie Tag Label Wrapped Around Manila Shipping Tags



Figure 11: Example Tie Tag Label Connected to the HPC, Cord Blood Cassette



17. ADDITIONAL INFORMATION:

On April 2, 2024, we requested the Applicant to submit the latest CAP (College of American Pathologists) proficiency testing record for (b) (4) for verification purposes. We also requested that the Applicant submit a copy of the accompanying records from a recent shipment of HPC, Cord Blood from StemCyte facility. Applicant provided the requested details on April 5, 2024, and they were reviewed by Dr. Mercy Quagraine, and found acceptable.