MEMORANDUM

BLA STN 125585
CMC Review of Original Submission
Product name: HPC, Cord Blood

Applicant: Bloodworks

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

Reviewed by:	Signature
Brian Niland, Ph.D. **Review Committee Chairperson**	
Prajakta Varadkar, Ph.D. **Product Reviewer**	
Heba Degheidy, Ph.D. **Product Reviewer**	
Joydeep Ghosh, Ph.D. **Product Reviewer**	
Safa Karandish, B.S., M.T. (ASCP) **Product Reviewer**	
Concurred by:	
Steven Oh, Ph.D. **Branch Chief**	

TABLE OF CONTENTS:

TABLE OF TABLES

TABLE OF FIGURES

EXECUTIVE SUMMARY

Recommendation:

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

BLA Submission History:

On June 8, 2011, a pre-BLA meeting was held with Puget Sound Blood Center (PSBC; now, Bloodworks) to discuss their plans to transition away from cord blood unit (CBU) processing using a (b) (4)

On February 27, 2012 the applicant implemented their (b) (4) processing change after the PSBC (now, Bloodworks) Cord Blood Services (CBS) department's cell processing facility (Seattle, WA) underwent reconstruction to allow for (b) (4) workflow and segregation of activities with subsequent and ongoing environmental monitoring.

On June 2, 2014, the applicant's first BLA (b) (4)) was submitted; however, it did not include stability testing data and resulted in a July 14, 2014 refuse to file (RTF) letter.

On January 28, 2015, the applicant submitted their second BLA (STN 125585), and included stability data as well as the applicant's responses to several additional information requests per our July 14, 2014 RTF letter.

On October 1, 2015, the applicant was informed that, with respect to use of cleared diagnostic tests (e.g. (b) (4) for syphilis donor testing), effective March 2016, cleared or approved diagnostic tests will no longer be considered to be adequate for use in donor testing for T. pallidum (per Guidance for Industry - Use of Donor Screening Tests to Test Donors of Human Cells, Tissues and Cellular and Tissue Based Products for Infection with *Treponema pallidum* (Syphilis) - published September 2015). In response to the information request dated 10/1/15 (Amendment 2), the applicant confirmed that the (b) (4) will be replaced with the (b) (4)) test, which is a cleared donor screening test for syphilis, by March 6, 2016. The plan is acceptable and the new test information can be submitted in the Annual Report.

On December 1, 2015, the applicant submitted an updated Form FDA 356h to notify FDA of their name change from Puget Sound Blood Center to "Bloodworks".

Product Overview

Hematopoietic Progenitor Cells, Cord Blood, (HPC, Cord Blood), manufactured by the Bloodworks CBS are minimally manipulated and unrelated allogeneic human cord blood cells. The applicant uses the (b) (4) system to reduce the plasma volume and the red

blood cells (RBCs) for all of the cord blood units (CBUs) collected. The CBUs are cryopreserved in 10% dimethyl sulfoxide (DMSO) containing 1% Dextran 40 using the controlled-rate freezer and stored in either the (b) (4) or liquid phase of the liquid nitrogen freezer after purity, identity, sterility and potency tests.

The shelf life of the HPC, Cord Blood under this BLA is determined to be two (2) years after the HPC, Cord Blood units are cryopreserved. This determination was made based on the stability data submitted by the applicant. There is an ongoing (b) (4) .

The HPC, Cord Blood units are shipped to the transplant centers frozen using validated "dry shippers" that are charged with liquid nitrogen (LN2) to maintain the temperature at ≤ -150^{o}C during shipping. The shippers are equipped with temperature recorders to record and document the temperatures throughout shipping period.

The applicant's updated thawing and infusion preparation instructions (e.g. wash step) are reflected in the applicant's revised prescribing information (PI) label and appended "Instructions for Preparation for Infusion" section.

Review Findings

The review team identified issues during review and inspection. All issues were communicated to the applicant through letters, teleconferences and during inspection. Of note, while correction of the applicant's sterility assay validation deficiencies (e.g. (b) (4)) was protracted, on November 11, 2015 the applicant re-submitted their sterility validation. As such, all corrected deficiencies and amendments to the application were found to be adequate by the review team. Based on the review of the information submitted in the original submission and 5 amendments, the review team has determined that the HPC, Cord Blood manufactured by the applicant met all the CGMP requirements and recommendations of the cord blood licensure guidance; therefore, the review team recommends approval of this BLA.

GENERAL INFORMATION

Bloodworks has applied for a biological license to distribute HPC, Cord Blood. HPC, Cord Blood is manufactured by Bloodworks' Cord Blood Services department (Bloodworks CBS) laboratory.

The Bloodworks CBS facility is where the CBUs are received, processed, cryopreserved, and stored in quarantine and long-term storage. The quality tests are performed at Bloodworks CBS, and other contract facilities as listed under testing facilities below and in the lot release testing section of this review. The applicant is American Association of Blood Banks (AABB) accredited and the Bloodworks Donor Testing Laboratory and Bloodworks Compatibility Laboratory are CLIA certified. The HLA lab is CLIA & ASHI accredited. The processing facility and permanent storage facility are located at:

Bloodworks
921 Terry Ave., Seattle, WA 98104
Phone: (206) 689-6301
Fax: (866) 261-5228
Registration (FEI) # 3071347
Establishment DUNS # 092881085

TABLE 1. List of Testing Laboratories

Lab name and location	Tests performed	Certificates/Accredits
Bloodworks Compatibility Lab (b) (4)	ABO/Rh blood type	CLIA 50D0661429
Bloodworks Donor Testing Lab (b) (4)	Infectious disease testing	(b) (4)
Bloodworks Lab (b) (4)	Sterility	AABB Accreditation Cert. (exp 3/31/16)
(b) (4))	Hemoglobinopathy test	(b) (4)
(b) (4)	Hemoglobinopathy test	(b) (4)
Bloodworks Compatibility Lab (b) (4)	Total nucleated cells count	CLIA#: 50D1014714
Bloodworks Lab (b) (4)	Nucleated cell viability	AABB Accreditation Cert. (exp 3/31/16)
Bloodworks Lab (b) (4)	Viable CD34+ cells	AABB Accreditation Cert. (exp 3/31/16)
Bloodworks Lab (b) (4)	Colony forming unit assay	AABB Accreditation Cert. (exp 3/31/16)
(b) (4)	HLA Typing (Initial Typing), Through NMDP	(b) (4)
(b) (4)	HLA Typing (Confirmatory), Through NMDP	(b) (4)

Applicant Contact Information:

Primary Contact:
Dr. Rebecca Haley, Medical Director, Blood Services and Cord Blood Services (CBS)
Bloodworks
921 Terry Ave., Seattle, WA 98104
Office phone: (206) 689-6301
Fax: (866) 261-5228
Email: BeckyH@BloodWorksNW.org

Secondary Contact:
Lisa R. Upshaw, Regulatory & Compliance Mngr., Quality Assurance & Regulatory Affairs
Bloodworks
921 Terry Ave., Seattle, WA 98104

Office phone: (206) 689-6355
Email: LisaU@BloodWorksNW.org

TABLE 2. Review Team

Discipline	Name
Product Reviewer/Chair (manufacture & process validation)	Brian Niland
Product reviewer (shipping, testing & assay validation)	Prajakta Varadkar
Product reviewer (DE, collection, & tracking)	Safa Karandish
Product reviewer (CD34+ flow cytometry)	Heba Degheidy
Product reviewer (sterility assay & validation)	Joydeep Ghosh
Pharm/Tox Reviewer	Jinhua Lu
Clinical Reviewer	Agnes Lim
RPM	Ramani Sista
Labeling Reviewer	Loan Nguyen; Dana Jones
DMPQ Reviewer	Richard Heath Coats
ORA/District Office Reviewer	Peter Kessler
Statistics Reviewer	Yuqun (Abigail) Luo

BACKGROUND/HISTORY

Bloodworks CBS is the manufacturer of the minimally manipulated, unrelated placental/umbilical hematopoietic progenitor cells, (HPC, Cord Blood), under this license application. The applicant has 16 years history of cord blood banking prior to the submission of this BLA. Prior to the use of the (b) (4) processing method on February 27, 2012, there were (b) (4) CBUs (b) (4) processed and banked. The applicant is seeking licensure of the CBUs that are manufactured using only the (b) (4) method and that meet the licensure requirements. Units in inventory that do not meet licensure requirements will be distributed under IND-7555 which is sponsored by the National Marrow Donor Program (NMDP).

CORD BLOOD BLA CHECKLIST

TABLE 3. Checklist (abbreviated)

Administrative requirement	Yes
HCT/P registration (FEI) #	Yes
Form 356h	Yes
Index	Yes
Representative draft labeling	Yes
A summary of the information submitted in the application	Yes
Chemistry, manufacturing and controls information	Yes
Validation Summary	Yes
Facility Description	Yes

Reviewer comment: *The team completed the filing checklist (see separate document) and all filing issues were resolved before the filling decision date. The application was filed.*

HPC, Cord Blood Product Description:

The applicant states that Hematopoietic Progenitor Cells, Cord Blood (HPC, Cord Blood) consists of HPCs, monocytes, lymphocytes, and granulocytes from human cord blood and is intended for intravenous infusion. The applicant states that while the active ingredient consists of CD34+ hematopoietic progenitor cells, the cellular composition of HPC, Cord Blood depends on the composition of cells recovered from the umbilical cord and placenta of the donor.

HPC, Cord Blood units processed and issued by Bloodworks Cord Blood Services (CBS), Seattle, WA are minimally manipulated and unrelated allogeneic human cord blood cells that contain live human cord blood cells after volume reduction and partial red cell and plasma depletion. Bloodworks uses the (b) (4)

The applicant contracts with 17 collection site hospitals located in the states of Washington, Oregon, and Hawaii. Cord blood collection is performed in-utero, before the placenta delivery in participating hospitals' labor and delivery area. Voluntarily donated umbilical cord blood (recovered from umbilical cord) is collected into a bag containing (b) (4) The collection bag is packaged and transported in a validated shipping container under temperature-monitored conditions (b) (4) to Bloodworks for (b) (4) processing and cryopreservation.

Pre- and post-processing samples are taken for in-process and final lot release testing including TNC, Viability, CD34%, CFU, ABO/Rh, HLA and sterility. Retention samples including plasma, RBCs and nucleated cells are taken after processing, before cryopreservation.

The processed CBUs are cryopreserved in 10% DMSO containing 1% Dextran 40 using a controlled-rate freezer, and stored in quarantine in LN2 freezer (b) (4) The final products are transferred to the on-site permanent storage location and stored at ≤-150^{o}C after all release criteria are met. At this time, the CBUs are eligible for listing in a searchable NMDP database so that transplant centers can match the CBUs with patients who need transplants.

HPC, Cord Blood has the following inactive ingredients: citrate phosphate dextrose (CPD), hydroxyethyl starch, DMSO, and Dextran 40. When prepared for infusion according to dilution instructions, the infusate contains the following inactive ingredients: CPD, (b) (4), DMSO, Dextran 40, and human serum albumin.

The labeling of each individual HPC, Cord Blood unit manufactured by Bloodworks CBS provides information about the total nucleated cells, post-processing viability, and number of viable CD34+ cells contained in the unit. It also contains ABO, Rh and HLA typing information. Each unit of "HPC, Cord Blood" contains a minimum of 5×10^8 total nucleated cells (TNC) with a minimum of 1.25×10^6 viable CD34+ cells at the time of cryopreservation.

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

Proprietary Name: The applicant does not have a proprietary name

Non-proprietary Name: HPC, Cord Blood

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

Inactive Ingredients:	**UNII Code:**
(b) (4) Citrate Phosphate Dextrose ((b) (4) ; see components below) (b) (4)	
Hydroxyethyl starch (HES)	(b) (4)
Dimethyl Sulfoxide (DMSO)	(b) (4)
Dextran 40	(b) (4)

Therapeutic or Pharmacologic Class: allogeneic cord blood HPC therapy

Dosage Form: Injectable Suspension
Route of Administration: Intravenous

NDC #: The applicant requested an NDC code exemption per applicant's use of ISBT 128.
The ISBT 128 facility code: (b) (4)
The ISBT 128 product code: (b) (4)

TABLE 4. Bloodworks Lot Release Criteria for HPC, Cord Blood

Product Characteristics	Testing Required	Tests Performed	Sample (Type and Timing)	Results of Product Testing

Safety	Infectious diseases	Anti-Hep B core; Anti-HCV; HBsAg; Anti-HIV-1/2; Anti-HTLV-I/II; Syphilis; HIV-1/HCV/HBV Nucleic Acid Test; Anti-CMV; WNV Nucleic Acid Test; Anti- *T. cruzi* (Chagas Disease)	Maternal peripheral blood obtained within 7 days of cord blood collection	All relevant communicable disease tests negative; CMV results are reported
	Sterility - Bacterial and fungal cultures	(b) (4)		No growth (aerobic or anaerobic)
	Hemoglobin		(b) (4)	No homozygous or double heterozygous hemoglobinopathy
Purity and Potency	Total nucleated cells (TNC)	(b) (4)	HPC, Cord Blood (pre-cryopreservation)	≥ 5.0 x 10^8 TNC
	Viable nucleated cells	(b) (4)		≥ 85% viable nucleated cells
	Viable $CD34^+$ cells (flow cytometry)	(b) (4)		≥ 1.25 x 10^6 viable CD34+ cells
	(b) (4)			

Identity	Human leukocyte antigen (HLA) typing (Initial)	[redacted]	(b) (4)	Report
	Confirmatory HLA typing	(b) (4)	Attached segment of HPC, Cord Blood at time of confirmatory typing	Confirms initial typing
	Blood group and Rh type	ABO/Rh type (performed by Bloodworks)	[redacted]	(b) (4)

CORD BLOOD COLLECTION

Bloodworks, Cord Blood Services (Bloodworks CBS) currently collects cord blood units at 17 hospitals in 3 states (Washington: 10 sites, Oregon: 1 site, Hawaii: 6 sites). Cord blood is collected by trained healthcare providers in both vaginal and C-section deliveries, following the Bloodworks CBS in-utero collection procedure (SOP CBP 4030, Instructions: 25-9-201 and 25-9-202).

Collection sites

The following is the current list of collection sites:

TABLE 5. Collection Sites

	Collection Hospital	Address
1	Evergreen Health Medical Center	12040 NE 128th St, Kirkland, WA 98034
2	Overlake Hospital Medical Center	1035 116th Ave NE, Bellevue, WA 98004
3	Northwest Hospital & Medical center	1550 B 115th St, Seattle, WA 98122
4	Swedish Medical Center- First Hill Campus	747 Broadway, Seattle, WA 98122
5	Swedish Medical Center- Ballard Campus	5300 Tallman Ave NW, Seattle, WA 98107
6	Swedish Medical Center- Issaquah Campus	751 NE Blakely Dr, Issaquah, WA 98029
7	Madigan Army Medical Center	9040 Jackson Ave, Tacoma, WA 98431
8	Oregon Health & Science University	3181 SW Sam Jackson Park Rd, Portland, OR 97239
9	MultiCare Tacoma General Hospital	315 M.L.K. Jr Way, Tacoma, WA 98405
10	MultiCare Good Samaritan Hospital	401 15th Ave SE, Puyallup, WA 98001
11	MultiCare Auburn Medical Center	202 N Division St, Auburn, WA 98001
12	Castle Medical Center	640 Ulukahiki St, Kailua, HI 96734
13	Kapiolani Medical Center for Women and Children	1319 Punahou St, Honolulu, HI 96826
14	Kaiser Permanente Medical Center	3288 Moanalua Road, Honolulu, HI 96819
15	Maui Memorial Medical Center	221 Mahalani St, Wailuku, HI 96793

16	The Queen's Medical Center	1301 Punchbowl St, Honolulu, HI 96813
17	Tripler Army Medical Center	1 Jarrett White Rd, Honolulu, HI 96589

Reviewer comment: *The applicant was asked to provide an updated list of collection sites (information request dated 10/1/15) because discrepant information was identified in different sections of the original submission. The above list was submitted in Amendment 2.*

Collection partner:
Bloodworks currently has one collection partner in Hawaii:

1. Hawaii Cord Blood Bank: 1319 Punahou Street, Honolulu, HI 96826

Reviewer comment: *In response to the FDA's letter dated July 18, 2014, Bloodworks explained that collection partners manage the collection sites. Each partnering organization has a signed formal contract or agreement with Bloodworks. Designated staff at these organizations is responsible for donor recruitment, obtaining donor screening information, training of collectors, managing collection supplies, and facilitating shipment of the collected units to Bloodworks (BLA module 1, 1.6.4 letter response). In the original submission, the applicant had listed 3 collection partners, one in each state where cord blood is collected (Hawaii, Washington, Oregon). In Amendment 2, the applicant listed only one collection partner located in Hawaii. The applicant was asked (request dated 11/12/15) to clarify who is responsible for managing collection sites in Washington and Oregon, since Bloodworks no longer has collection partners in those two states. In Amendment 3, the applicant explained that for hospitals in Washington, Bloodworks staff is responsible for managing the collection sites. For the one collection hospital in Oregon, Bloodworks has a trained Donation Coordinator who is employed by the hospital and is responsible for training the healthcare providers and managing the collection supplies. The Donation Coordinator at Bloodworks is responsible for obtaining donor screening information for collections that are performed at the hospital in Oregon. The described process is acceptable because Bloodworks has the overall responsibility for management of activities at the collection sites, and collected units that don't meet the initial acceptance criteria are discarded.*

Collection Site Qualification

Hospitals that participate in the cord blood collection program must have a signed Memorandum of Agreement (MOA) with Bloodworks (SOP CBP 1031). Each collection site is qualified initially before any collection activity begins and (b) (4) . The collection site qualification includes the following elements (SOP CBP 2080):

- Signed MOA
- Participation in an external accreditation program such as the Joint Commission
- Designated storage area that meets the security and storage temperature requirements (b) (4) for cord blood collection kits and secure cord blood pick-up area
- Evaluation of transportation arrangements that meet chain of custody criteria (for new collection sites, a transportation trial run is conducted).
- Cleaning procedures

- Maternal specimen collection practices and procedures
- Collector training

Collection site qualifications are documented on the HPC, Cord Blood Collection Site Qualification Checklist (25-9-149). Depending on the findings and the result of corrective actions, collections will stop at the facilities that fail the (b) (4) requalification.

Reviewer comment: *The collection site qualification process is acceptable.*

Collection Site Staff Training

Cord blood is collected by healthcare providers (MDs, Nurses, Midwives, and OB Techs) at the delivery hospitals. Collectors are required to complete an initial training and an (b) (4) competency program (SOPs CBP 3000 and CBP 3005).

Initial training is conducted in-person or via web-based presentations. Collectors are trained on: 1) donor recruitment and enrollment, 2) assessing birth mother's and baby's suitability for donation and the exclusion criteria 3) collection and packaging supplies, 4) collection procedure, 5) obtaining consent and completion of forms and documentation, 6) packing and transportation, 7) obtaining and documenting the relevant medical record information on the birth mother and the baby for donor screening purposes. Trainees must successfully pass a test. Retraining is conducted as deemed necessary. For (b) (4) competency, collectors must complete a written assessment. Training records are maintained in the local Bloodworks computerized "Cord Blood Collector Training Database."

Cord blood units collected by individuals who have not completed the initial training or the required (b) (4) competency are discarded upon receiving the units and reviewing the records at Bloodworks. Additionally, trained collectors are notified if they collect a cord blood unit that is not qualified for banking (e.g. collection from a minor or twin delivery, <37 weeks gestation, or a unit that subsequently test positive for microbial or fungal contamination). Collectors who perform the same unqualified collection a second time are required to complete an in-person training session.

Reviewer comment: *The training procedure is acceptable.*

Donor Recruitment, Pre-screening and Consent

Bloodworks recruits potential donors during the prenatal or at the time of admission to the labor and delivery unit at the hospital (SOP CBP 3010). Educational materials are provided to the birth mothers. The donor outreach activities also include conducting in-services for the medical professionals. Enrollment for the cord blood donation program can occur online at the Bloodworks website or by contacting the cord bank directly as early as 6 weeks prior to the delivery date, or on the day of hospital admission. Birth mothers must meet the following criteria to qualify for enrollment:

- At least 37 weeks gestation
- 18 years of age or older
- Singleton birth
- Delivery at a participating hospital with trained staff
- No health history of cancer, blood disease or disorder in either of the baby's parents or any of the baby's siblings.

Mothers must sign a consent form prior to collection of cord blood. Consent can be obtained by the Donation Coordinators or trained healthcare providers when the mother is not in active labor.

Collection Supplies

Collection supplies and reagents are inspected and evaluated to ensure that they meet pre-established criteria before being released for use (SOP CBP 2070). Pre-assembled collection kits that include the necessary supplies for cord blood collection are provided to each participating hospital in insulated transportation containers. The containers include a temperature monitoring device that is affixed to a gel wrap. Each collection kit consists of cord blood collection bag, plastic tubing clamp, needle protector, (b) (4), sliding clamp, vacutainer tubes for collection of maternal samples, enrollment packet (includes instructions, cord blood donor short screen and update form, consent form), and the in-hospital documentation packet (includes collection instructions, delivery information from, maternal sample collection form, and label). The lot# and expiration date of supplies are documented and lot # is assigned to each pre-assembled collection kit (SOP CBP 4010).

Cord blood is collected in (b) (4) collection bags (manufactured by (b) (4) product code: (b) (4) that contain (b) (4) C-section Adapter kits are also provided to the hospitals for cord blood collections in cesarean deliveries. An example of the manufacturer's certificate of analysis for the collection bag and the sterilization report for one lot of the C-section adapter kits was submitted in the application.

Reviewer comment: *The name of the manufacturer for the C-section adapter kit was not included in any of the documents that were submitted in the original application. In an email response dated 12/1/2015, the applicant stated that the adaptors (part #* (b) (4) *) are manufactured by* (b) (4) *. and provided the Material Specification document. The applicant was asked to submit this information and it was received in amendment 4.*

Collection Procedure and Contamination Controls

Bloodworks has established the following controls for the collection procedure (SOP CBP 4030):

1. Pre-assembled cord blood collection kits are stored at (b) (4) in designated storage area at each collection hospital.

2. Cord blood is collected in both vaginal and C-section deliveries, before the placenta is delivered (in-utero collection). For C-section deliveries, collection is performed in the sterile field using the C-section Adapter kit.
3. Birth mothers identity is verified by asking her name and checking the information on her hospital issued wristband.
4. To minimize risk of contamination, cross contamination or mix-up:
   - single use, sterile collection bag and supplies are used for collection.
   - collection bag is inspected for damage or defects before starting the procedure.
   - collection bag is pre-labeled with mother's hospital generated identification label.
   - the venipuncture site on the cord is disinfected with (b) (4) (vaginal deliveries only).
   - cord blood is collected into the collection bag by (b) (4) during collection.
   - relevant information on the birth mother and the newborn (e.g. name, hospital medical record number, date of birth, gestational age, baby's sex), cord blood collection date and time, type of delivery, delivery complications, and the collection staff identity are documented on the Delivery Information form (25-9-021).
   - collected cord blood unit and maternal specimens are placed in separate zip-lock bags and packaged in transport containers prior transportation

Reviewer comment: *The collection procedure and the established controls are acceptable.*

Storage and Transportation of Collected Cord Blood Units

Collected cord blood units are individually packaged and stored in designated areas at the collection site prior to transportation to the processing laboratory. The collected unit and the associated maternal samples are placed in a gel wrap that is attached to a temperature monitoring device. The unit and the gel wrap assembly are then placed in an insulated envelope. The envelope is sealed and placed in the transport container along with the associated documents per SOP CBP 4070 and BLA module 3: 3.2.S.2.2.1.4. For additional details, please see the shipping validation section of this review.

For local collection sites (defined as participating hospitals is Western Washington), the units are transported in (b) (4) Plastic Kits that are qualified to maintain temperature between (b) (4) . Bloodworks Transportation Department couriers pick up the collected units from the local hospitals. For long distance collection sites (defined as participating hospitals outside the Western Washington area or out of state), the units are transported in (b) (4) Insulated Shipping kits that are qualified to maintain temperature between (b) (4) . Contract courier companies are used for transporting units from the long distance collection sites. The units collected at hospitals in Hawaii are transported by companies that provide door-to-door transportation service which includes use of ground couriers and airline carriers. The chain of custody is maintained and documented throughout all transportation stages. All cord blood shipments are received by Bloodworks Order's Processing

Department which is staffed 24 hours every day. The transport containers are stored at (b) (4) until they are picked up by the processing laboratory staff. The collected units are evaluated and accepted for processing, if they are received by the processing laboratory within (b) (4) of collection as per SOPs CBP 4010, CBP 4070, CBP 4060, and BLA module 3: 3.2.S.2.2.1.5.

Reviewer comment: *Any unit that is not transported within the acceptable temperature range is either discarded or used for research. For additional details, please see the shipping and transportation validation section of this review. The storage and transportation procedure is acceptable.*

Initial Cord Blood Qualification Criteria

Upon receipt, cord blood units are evaluated and documentation is reviewed to ensure that the units are acceptable for processing per SOP CBP 4060. The following is the summary of the initial acceptance criteria per SOPs CBP 4060 and CBP 1060:

- Collection bag properly labeled with birth mother's identification information
- Transport temperature within acceptable range
- Bag damage, leak or clots not observed
- Pre-processing volume: (b) (4)
- Receipt of the unit within (b) (4) of collection

Reviewer comment: *In the original BLA, discrepant information was provided regarding the minimum acceptable pre-processing cord blood volume: 1) Draft SOP 1060:* (b) (4) *2) BLA module 3, section 3.2.S.2.4:* (b) (4)*, 3) Form 25-9-203, "CBU Initial Receipt":* (b) (4) *for Hawaii units,* (b) (4) *for non-Hawaii units. In Amendment 2, the applicant clarified that the current minimum acceptable volume is* (b) (4) *for all units and submitted the revised Form 25-9-203 and final SOP CBP 1060. The response is acceptable.*

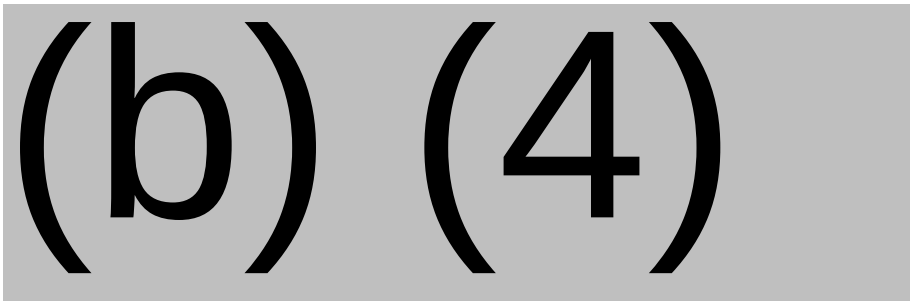
COLLECTION VALIDATION

Bloodworks submitted a summary of the collection validation in the original application (BLA module 3, 3.2.S.2.5). A total of (b) collections ((b) vaginal and (b) C-section deliveries) were performed by trained collectors following the established collection procedures. Each collection was observed by a Bloodworks collection staff and evaluated for the following parameters:

- Collection performed according to the instructions
- Units packaged and labeled correctly
- Documents and forms completed
- Lot numbers and expiration dates of supplies recorded and traced back to the lot # assigned to cord blood collection kit.

The (b) (4) collected units met the above criteria with two minor observations (e.g. lot # transcription error), which were resolved after follow-up investigation and SOP clarification.

The submitted summary of collection validation did not indicate whether the (b) (collected cord blood units met the minimum acceptable volume of (b) (4). The applicant was asked to submit additional information related to the unit volumes and any sterility assessments that were performed (email request dated 10/1/2015). In Amendment 2, the applicant explained that additional assessments were performed but due to inherent variability of cord blood collections; irrelevant of collector competency, they did not include all the evaluated parameters and reasons for discard in the original validation. They provided the following information for the (b) (4 units that were used for the validation:



One out of (b) (4) collected units did not meet the minimum pre-processing acceptable volume (b) (4). Units (b) (4) that met all the pre-processing acceptability criteria, (including (b) (4) were tested for sterility and the results were negative. The applicant also indicated that their rate for contamination is (b) (4).

Reviewer comment*: In the applicant's collection process summary section, i.e. BLA module 3, 3.2.S, the applicant explained that only about (b) (4) of their incoming units are typically processed, with low TNC being the most frequent disqualifying factor. Considering the expected variability in volume and TNC of collected cord blood units, the additional validation information is acceptable. Furthermore, collected units that don't meet the pre-defined acceptance criteria are either discarded or used for research.*

DONOR ELIGIBILITY DETERMINATION

Bloodworks' donor eligibility determination procedures include screening and testing of the cord blood donors for risks of relevant communicable diseases or disease agents (RCDADs).

Donor Screening

Bloodworks utilizes the NMDP's Cord Blood Maternal Risk Questionnaire, Family Medical History Questionnaire to obtain information about the donor's medical history. The medical history interview of the birth mother is conducted by trained staff (either on the phone or in person at the hospital) within 7 days before or 30 days after cord blood collection. If the

medical history interview is conducted greater than 7 days prior to the collection, changes in the medical history is obtained and documented at the time of collection (SOPs CBP 3050 and 3040). Bloodworks provides instructions to the healthcare providers who are responsible for collection of the cord blood to evaluate the birth mother and the infant donor for clinical and physical evidence of RCDADs (Delivery Information Form 25-9-021). The relevant information is documented on the cord blood Delivery Information Form. The hospital medical records are requested and reviewed by the cord blood bank staff for further evaluation of specific findings.

Furthermore, Bloodworks does not collect cord blood units if any of the following conditions or complications is present:

- Pus or placental trauma
- Excessive maternal bleeding
- Malodorous placenta or amniotic fluid
- Evidence of genital herpes or other infection, unless it is C-section delivery
- Fetal infection or malformation including metabolic disorders, chromosomal abnormalities or structural anomalies

Donors are screened for risk factors associated with HIV 1 and 2, HBV, HCV, Syphilis, HTLV I and II, WNV, Sepsis, Vaccinia, TSE (CJD/vCJD), and xenotransplantation. In addition, donors are screened for parasitic blood diseases (malaria, Leishmaniasis, Chagas disease, Babesiosis) which are not currently required by the FDA.

Reviewer comment: *According to the information in the initial submission, for collections in Hawaii, trained collection partner staff located in that state are responsible for obtaining the donor screening information. The applicant was asked to clarify who is responsible for obtaining the donor screening information for the collection sites in Washington and Oregon. In the response letter submitted in Amendment 3, the applicant explained that for the Washington and Oregon sites, the Bloodworks cord blood donation coordinators are responsible for obtaining the donor screening information. The applicant has also submitted revised SOPs and forms: Amendment 2: Delivery Information Form 25-9-021, BLA Amendment 3: SOPs CBP 3050 and CBP 3040.*

Donor Testing

The infectious disease tests are performed by the Bloodworks Donor Testing Laboratory. The testing lab has a Medical Test Site License (no. MTSA.FDS.00001459) issued by the Washington State Department of Health, CLIA certification (no. 50D0869979), AABB accreditation and is under the blood center's FDA Establishment License (n. 192) (BLA module 3: 3.2.S.4.2).

Reviewer comment:

- *In the original submission, the CLIA certificate was not provided. In the response letter submitted in Amendment 1, the applicant explained that in the state of Washington, the CLIA certificate must be submitted to the State Department of Health, which in return, issues the certification of the laboratory practice. The updated state certificate which includes the CLIA number was submitted. The Puget Sound Blood Center (now,*

Bloodworks) donor testing laboratory is also registered with the FDA (FEI#: 3001617760).

- *The applicant's legal name changed from Puget Sound Blood Center Program operating under U.S. License Number 192 to Bloodworks under the new FDA issued License Number 2042. Letter from OBRR submitted in Amendment 4.*

Maternal blood specimens for donor testing are obtained by the hospital staff following Bloodworks' instructions. The maternal specimens are collected within 7 days of the infant's delivery. The blood collection tubes and the Maternal Sample Form are labeled with hospital generated labels which include the birth mother's name, medical record #, date of birth, phlebotomist's identification and date of sample draw. Information regarding transfusion of blood products and/or infusion of intravenous fluids is also documented on the Maternal Sample Form. Maternal blood specimens are not accepted for testing if the birth mother has received a transfusion of more than (b) (4) of blood, blood components within (b) (4) hours or more than (b) (4) within (b) (4) before the specimens for infectious disease testing are collected. Maternal specimens are transported with the collected units to the cord blood bank in containers that maintain temperature between (b) (4). Infectious disease testing is completed within (b) (4) hours of specimen collection. (SOPs CBP 1060, CBP 4065)

Birth mothers are tested for the following:

FDA required tests: Anti-HIV 1 and 2, HIV-1/HCV NAT, Anti-HTLV-I and II, HBsAg, Anti-HBc, Anti-HCV, Syphilis, Anti-CMV

A*dditional tests not currently required by the FDA*: WNV NAT, HBV NAT, Anti- *T. cruzi.*

The testing laboratory performs the tests using FDA-licensed, approved or cleared donor screening tests.

TABLE 7. Donor Infectious Disease Tests

Test	Trade Name	Manufacturer
Hepatitis B surface Antigen (HBsAg)	(b) (4)	
Hepatitis B core Antibody (HBc)	(b) (4)	
Anti-Hepatitis C (HCV)	(b) (4)	
Anti-Human T-Lymphotrophic Virus (HTLV)	(b) (4)	
Anti-Human Immunodeficiency Virus 1 and 2 (HIV)	(b) (4)	
HIV-1/HCV/HBV Nucleic Acid Test	(b) (4)	

Treponema pallidum (Syphilis)	(b) (4)	
	(b) (4)	
Cytomegalovirus (CMV) Antibody	(b) (4)	
	(b) (4)	
West Nile Virus (WNV) Nucleic Acid Test	(b) (4)	
Trypanosoma cruzi (Chagas Disease)	(b) (4)	

Bloodworks discards units from birth mothers who have positive or reactive results for the above donor screening tests, except for CMV (SOP CBP 1060). CMV results are reported to the transplant center.

The Donor Safety and Surveillance department at Bloodworks is responsible for notifying mothers who have a positive infectious disease test results (except for CMV). The steps for notification and counseling are defined in SOP SAS 0701. A copy of the notification letter is maintained in the cord blood unit batch record.

Reviewer comment: *The applicant is currently using a cleared diagnostic test for syphilis* (b) (4) *The applicant was informed that effective March 2016, cleared or approved diagnostic tests will no longer be considered to be adequate for use in donor testing for T. pallidum (refer to the Guidance for Industry- Use of Donor Screening Tests to Test Donors of Human Cells, Tissues and Cellular and Tissue Based Products for Infection with Treponema pallidum (Syphilis) - published September 2015). In response to the information request dated 10/1/15 (Amendment 2), the applicant confirmed that the* (b) (4) *will be replaced with the* (b) (4) *test, which is a cleared donor screening test for syphilis, by March 6, 2016. The plan is acceptable and the new test information can be submitted in the Annual Report. The applicant submitted the revised HPC, Cord Blood Criteria Policy (SOP CBP 1060) in Amendment 3.*

Final Donor Eligibility Determination

Bloodworks determines the donor to be eligible if the donor screening does not identify any risk factors for RCDADs and all the infectious disease test results are negative or non-reactive, except for CMV (SOP CBP 8040).

The medical director is responsible for reviewing all the screening and testing results and making the final donor eligibility (DE) determination before the unit is released to the searchable inventory. Bloodworks only accepts cord blood units from eligible donors for

licensure. The medical director completes and documents the final DE determination on the HPC, Cord Blood Release Specification for Inventory form (25-9-218). At the time of distribution to the transplant center, the summary of records which include the list of infectious disease test results (CBU Summary Form) and the Final Eligibility Determination form (25-9-179) accompany the unit.

Reviewer comment: *The donor eligibility determination is performed in accordance with the regulatory requirements. The applicant submitted the revised HPC, Cord Blood Final Eligibility Determination form (25-9-179) in Amendment 3.*

FACILITY DESCRIPTION, FLOOR DIAGRAMS, & CBU PRODUCT FLOW

(Please see DMPQ review for detail)

The Bloodworks facility contains (b) (4) square feet of office, medical, laboratory, storage/utility, and parking space in (b) (4) floors (b) (4) and (b) (4) floors (b) (4) The Bloodworks Cord Blood Services (CBS) department occupies space on (b) (floors of the Bloodworks facility: (b) (4)

All cord blood shipments are delivered to Bloodworks' Order Processing Department (OPD) which is staffed (b) (4) day and is specifically designated for receiving samples and blood products.

Cord Blood receipt, processing, testing, and product distribution facilities, as well as materials and product storage areas are located in the (b) (4) floor of Bloodworks, occupying a total of (b) (4) of floor space.

(b) (4)

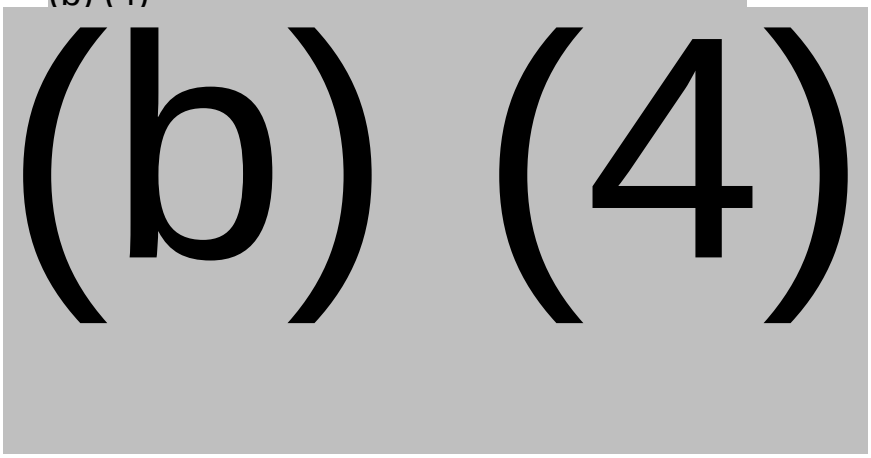


FIGURE 1. Bloodworks (b) (4) **CBU processing** (b) (4)

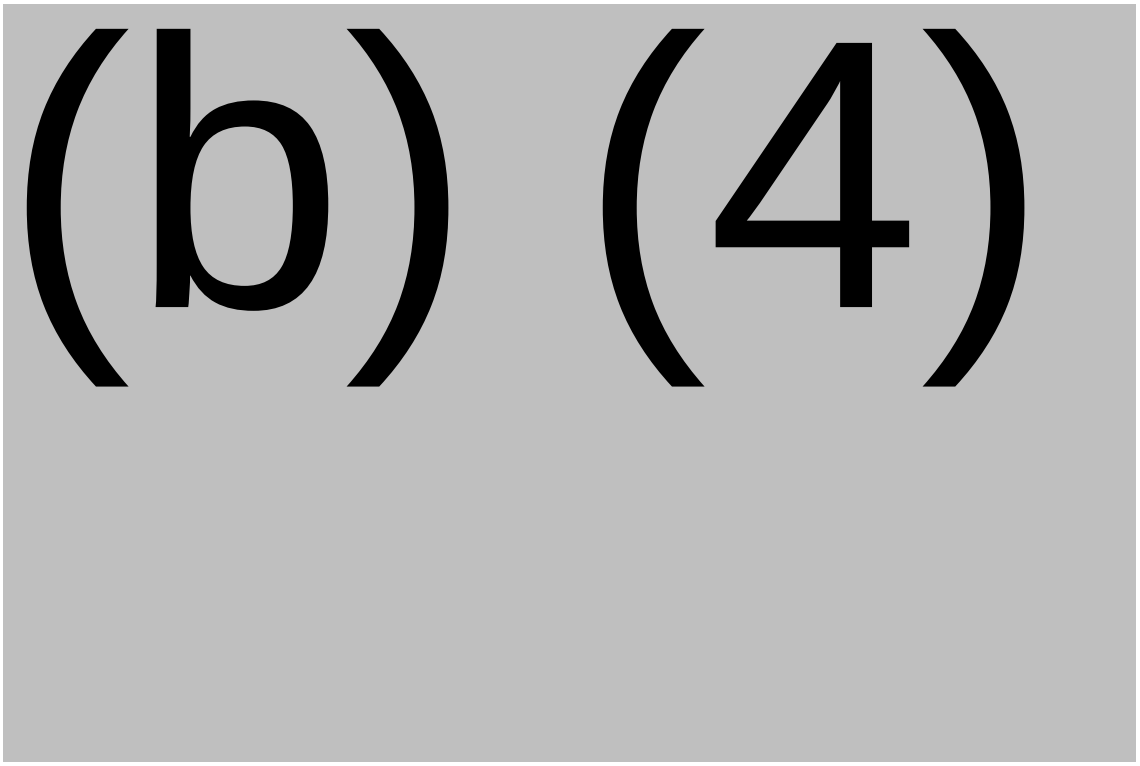
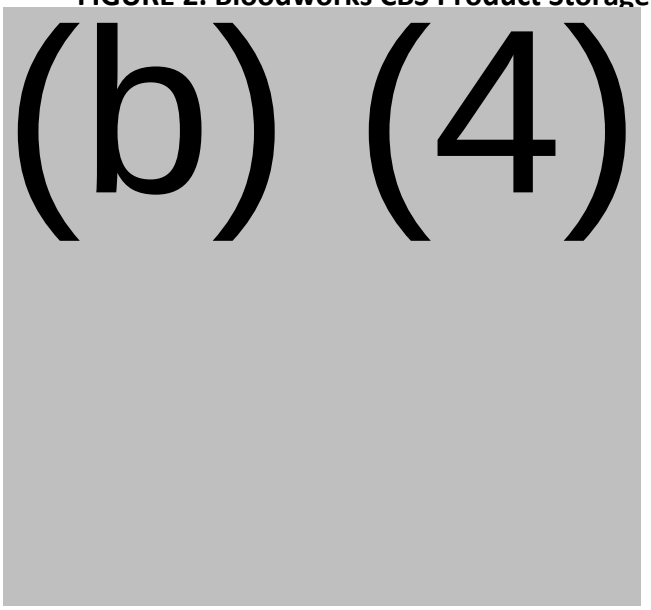


FIGURE 2. Bloodworks CBS Product Storage Room (b) (4)



• Receipt and Distribution Area (b) (4)):
Incoming CBUs are received, unpacked, and checked-in. Incoming CBUs with expected documentation are placed into unit segregation boxes with the transportation box number as identification until the HPC, Cord Blood unit Local DIN Barcoded Label is generated. These CBUs are transported from the receiving area to the "clean processing area" ((b) (4) for sampling.

• Cord Blood Services Cell Processing Laboratory (b) (4)):
(b) (4)
.

• Cord Blood/Product Testing Laboratory (b) (4)
(b) (4)

• Cord Blood Product and Materials/Supplies Storage (b) (4)
(b) (4)

• Cord Blood Services Product Storage (b) (4)
(b) (4)

CONTROL OF ASEPTIC MANIPULATIONS:
(Please see DMPQ review of aseptic process validation/media fill, and cleaning validation process)

• Contamination Precautions:
Manufacturing involves processing of CBUs (b) (4) . The applicant states a combination of engineering, physical, and procedural controls have been established to control cross-contamination of documentation, samples, supplies, or products.

• Engineering controls:
- HPC, Cord Blood manufacturing occurs in a secure and controlled environment ((b) (4)) with(b) (4) air quality requirements of (b) (4) document;
- Single-use disposable processing supplies and materials (i.e., "functionally closed" (b) (4) includes pre-connected FDA cleared (b) (4) are used to minimize the risk of contamination and cross-contamination during HPC, Cord Blood manufacture; biologic safety cabinet ((b) (4) used during test sample preparation;
- Single-unit at a time processing equipment (e.g. (b) (4) cryopreservation).

• Physical controls:
- CBU segregation bins (include all required forms, labels, and supplies);
- (b) (4) workflow to minimize cross-contamination risk and mix-up errors;
- Container closure system packaging components (e.g. overwrap bags, labeled storage cassettes) are used during cryopreservation, storage, and distribution;
- Quarantined CBUs and released HPC, Cord Blood products are maintained in separate LN2 freezers;
- HPC, Cord Blood manufacturing records, test results and process labels are secured in a batch record.

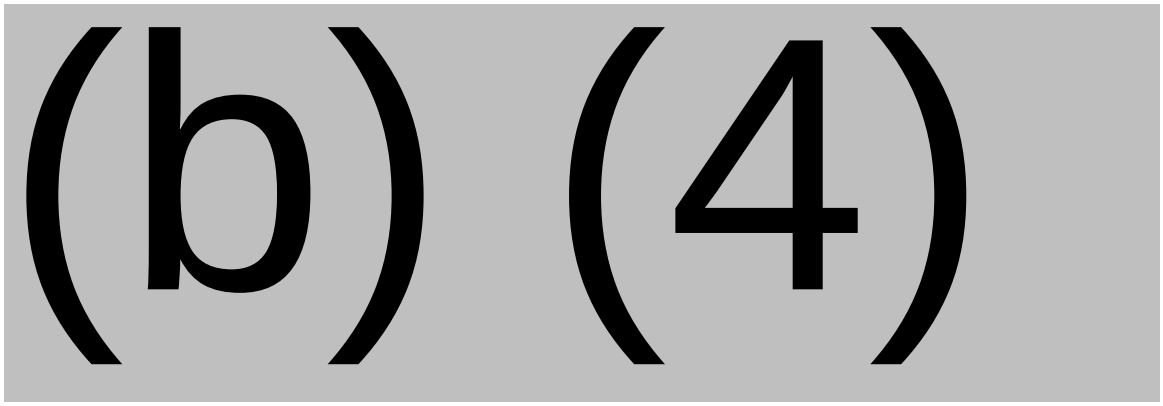
• Procedural controls:
- One-at-a time handling of cord blood units, materials, or documentation;
- Workstation inspection and clearance;
- Manufacturing equipment is cleaned with every use to prevent cross-contamination.

Control measures to minimize CBU contamination are contained in SOPs for the various processes.

Reviewer comment: *The applicant's in-process controls appear to adequately prevent contamination or cross-contamination.*

CONTAINER CLOSURE SYSTEM:

Cord blood is collected from the umbilical cord and placenta of a volunteer after the infant is delivered. The applicant states HPC, Cord Blood is collected in an FDA-cleared blood collection bag (table below) containing (b) (4) designed to hold (b) (4) of blood. The typical collections are between (b) (4) . The (b) (4) sterile, single-use processing kit is intended for CBU banking by the manufacturer and contains the remaining containers and closures associated with the cord blood processing. The applicant states this kit is a sterile, FDA-cleared, functionally closed system, including the final product bag (table below). The (b) (4) is composed of (b) (4) . The applicant uses a (b) (4) made of (b) (4) material intended to remain flexible in LN2 (b) (4) . Names of products used, their manufacturers, catalog order numbers and FDA approval or clearance reference numbers are below.



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

CORD BLOOD PROCESSING

Overview:
CBU processing from accessioning through product cryopreservation takes place in a controlled environment (b) (4) air quality; Class (b) (4) . This includes CBU evaluation, CBU number assignment, pre-processing CBU sampling (via sterile connect syringe with tubing), (b) (4) processing, cryoprotectant addition, finished Cord Blood product sampling and packaging. Key processing reagents, supplies, & equipment are listed below (Table 10).

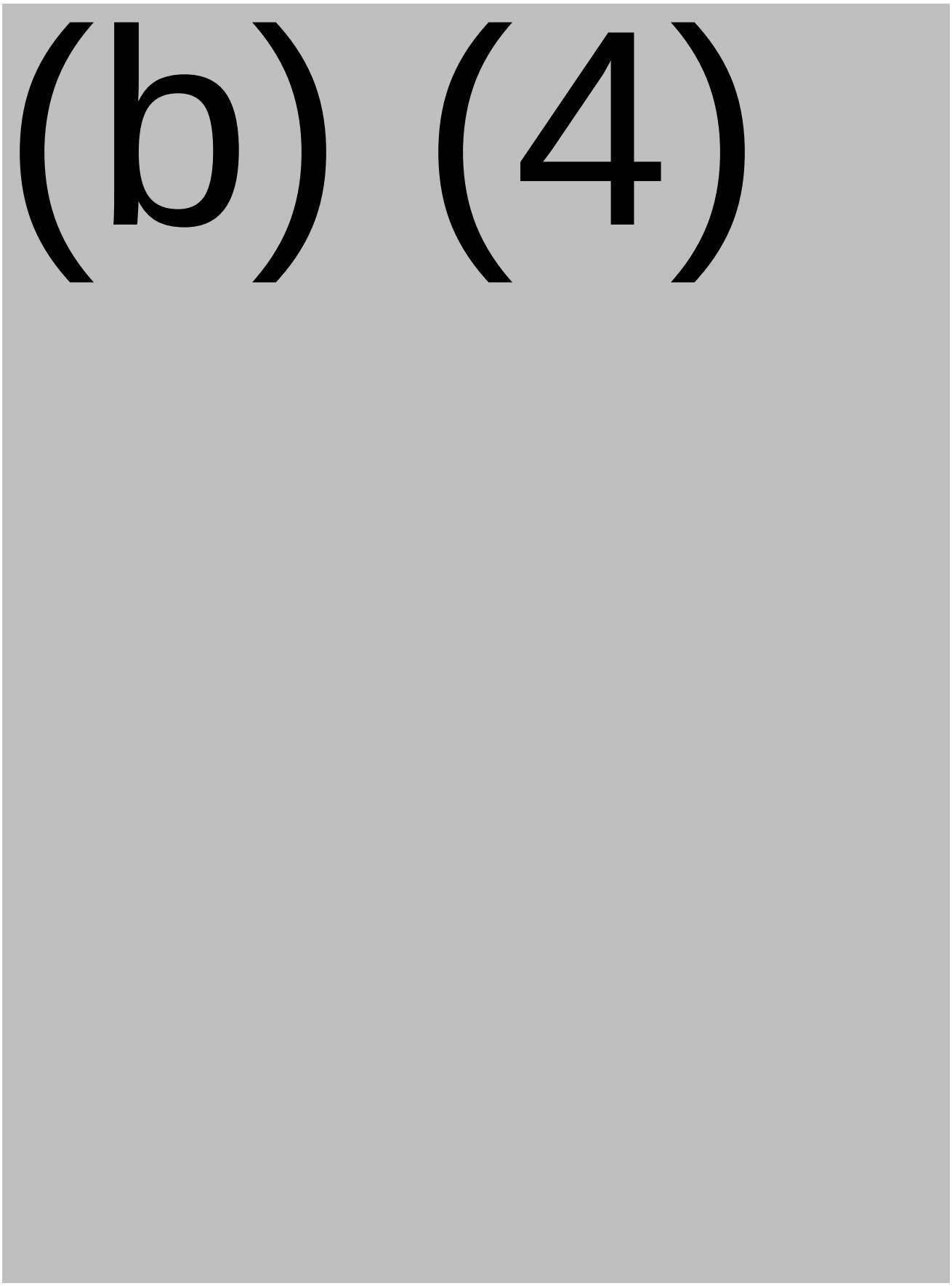
REAGENTS USED IN MANUFACTURE
Material Acceptance, Release, and Conformance Testing of Critical Reagents and Supplies:

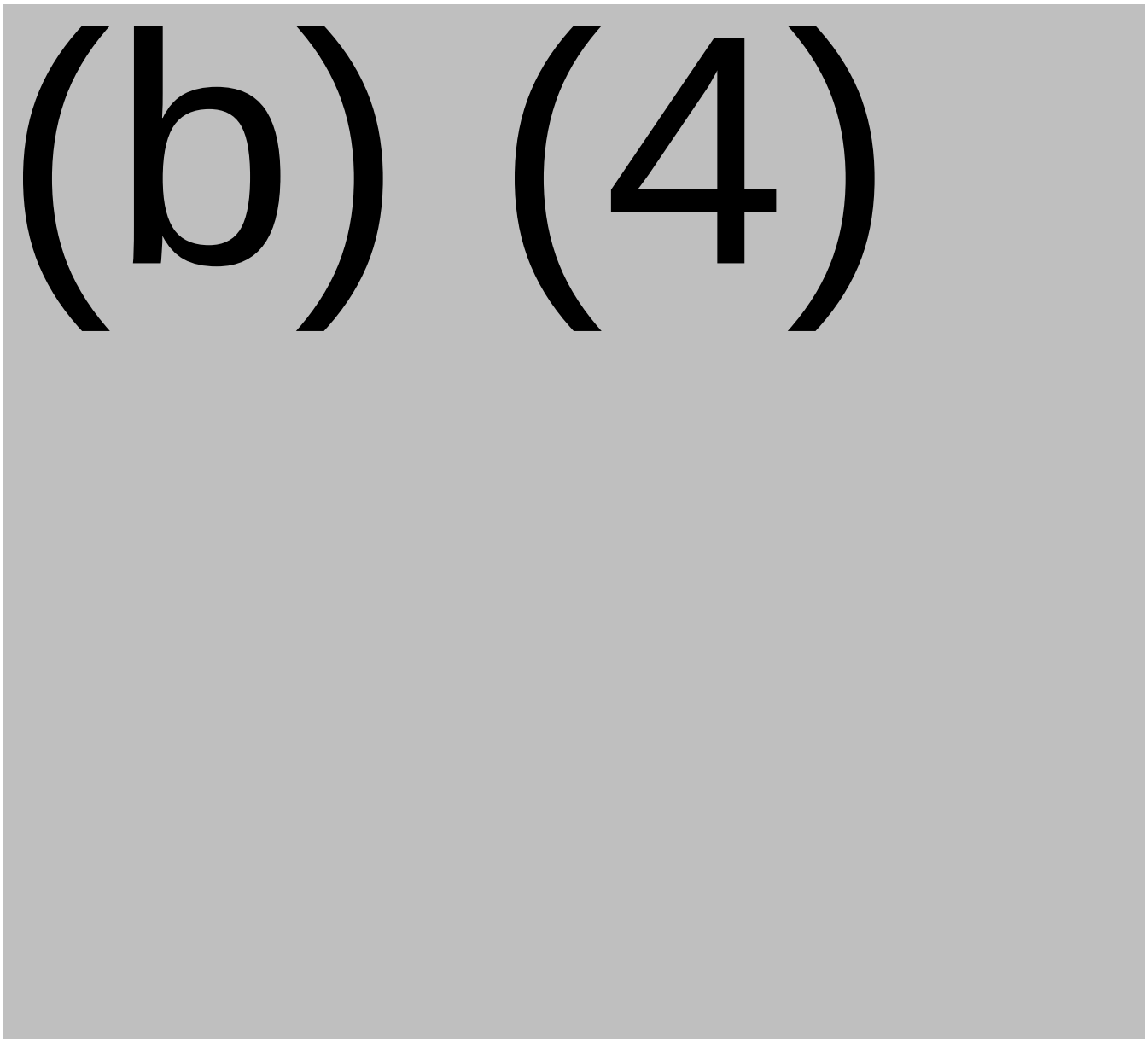
Bloodworks performs vendor qualification per SOP BCQ 0502, "Supplier Qualification Process" followed by an initial reagent validation. Initial reagent validation confirms that the provided material meets written specifications described in Bloodworks SOPs to qualify the reagent or material for use.

Following receipt and inspection (per SOPs CBP 2070 "Management of Critical Materials" and CBP 2071 "Critical Materials Specifications"), quarantined materials (i.e. requiring additional quality testing or manufacturer's evidence of quality or quality testing) are transported into Room (b) (4) and placed in a locked storage cage until release. Each received lot undergoes an initial assessment and release testing to qualify the supplied material for use in manufacturing.

In addition to acceptance testing of supplies and standards used in lot release testing (e.g. (b) (4) for sterility) BLOODWORKS performs sterility release of their sterile ready-to-use (b) (4) ; DMSO (b) (4), Dextran-40 (b) (4) and (b) (4) by (b) (4) must be sterile. Several key reagents and supplies are outlined in the Reference Table, below:

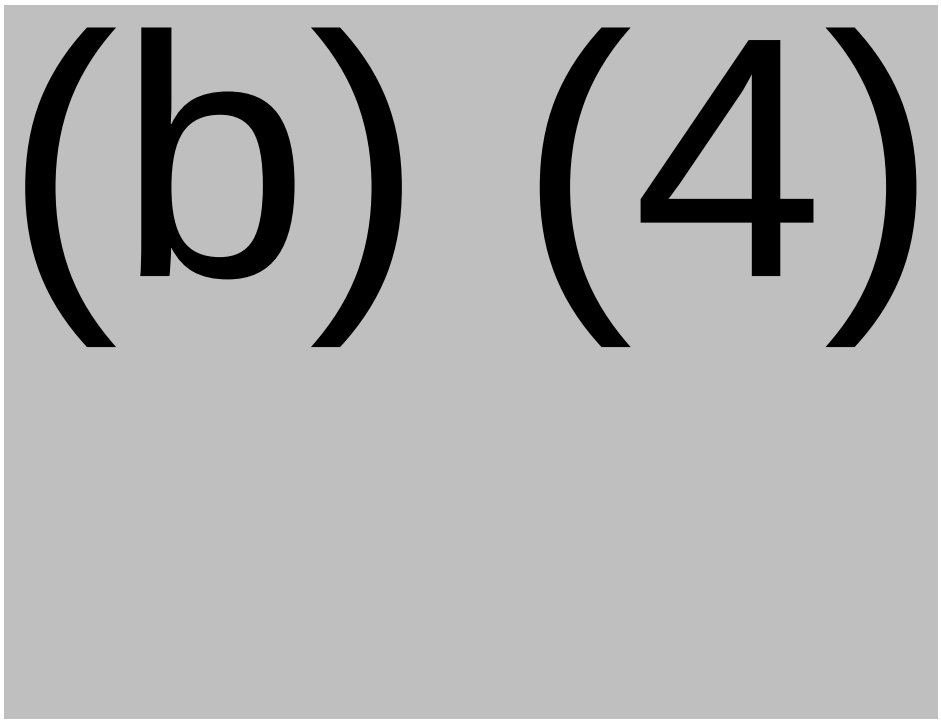
(b) (4)


(b) (4)



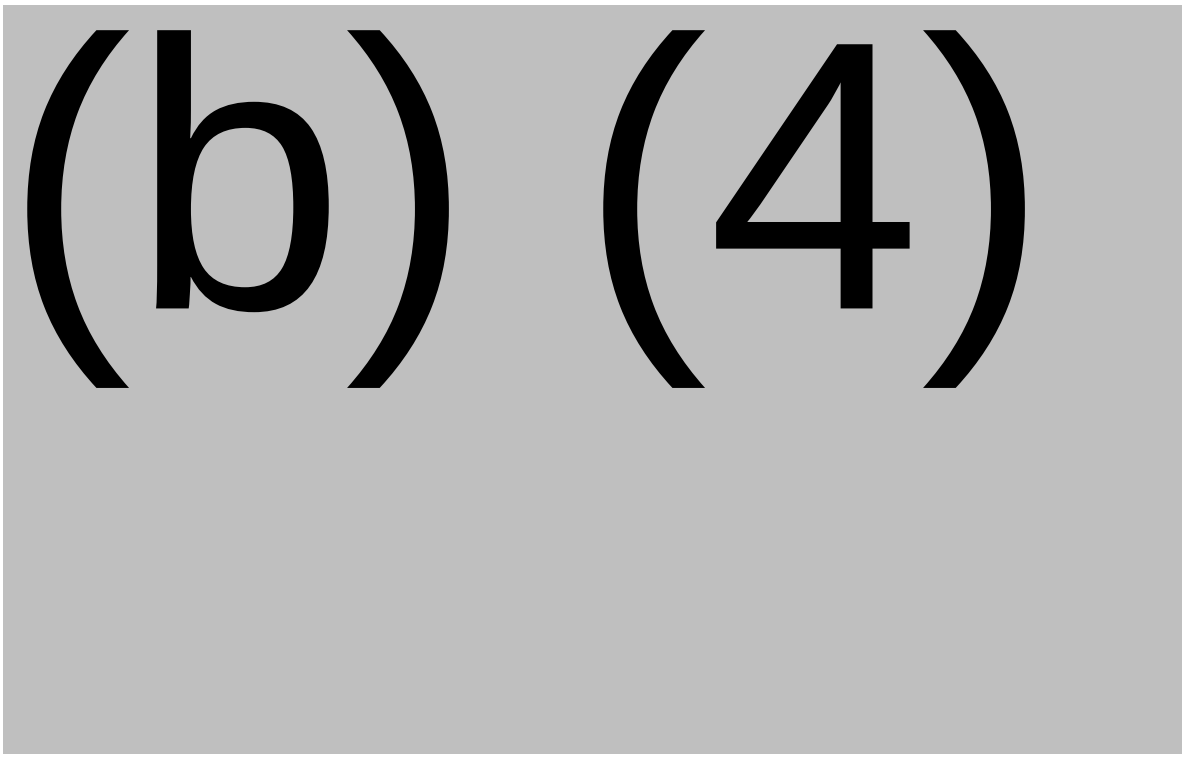
Processing by (b) (4)

Processing of qualified CBUs from the collected anticoagulated whole cord blood into a volume reduced, plasma-reduced and red cell-reduced buffy coat product occurs using the (b) (4) This CBU (b) (4) single-use disposable processing supplies and materials (i.e., "functionally closed" (b) (4) connections). The (b) (4) cell kit (Product (b) (4)) is shown below in Figure 3 (b) (4) Figure S.2.1-5). Of note, Figure 3 includes use of an (b) (4) Bloodworks uses a (b) (4) and is connected by sterile process above A in the diagram.



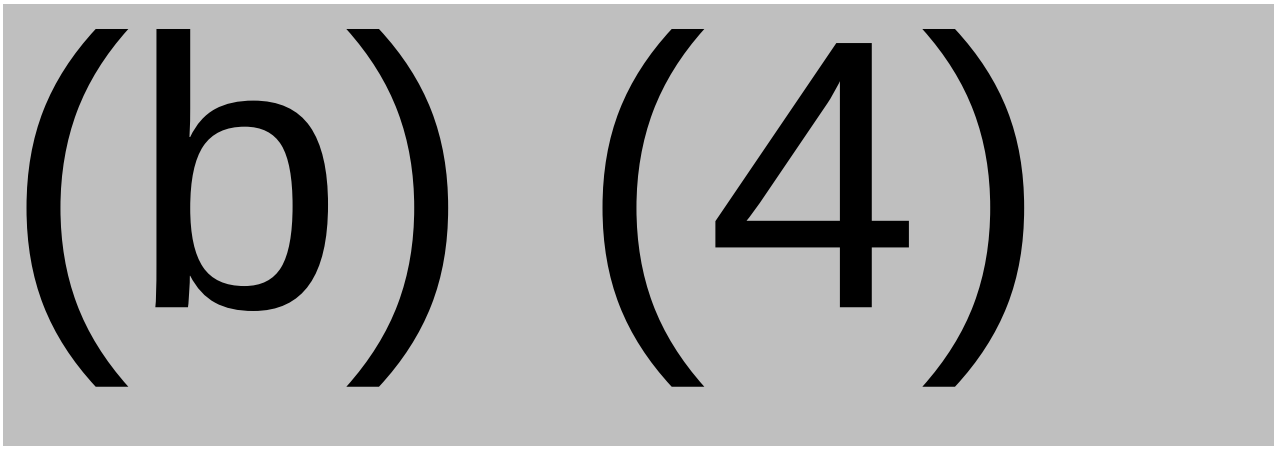
(Also, please reference Table 9. Listing of containers used during CBU collection & processing.)

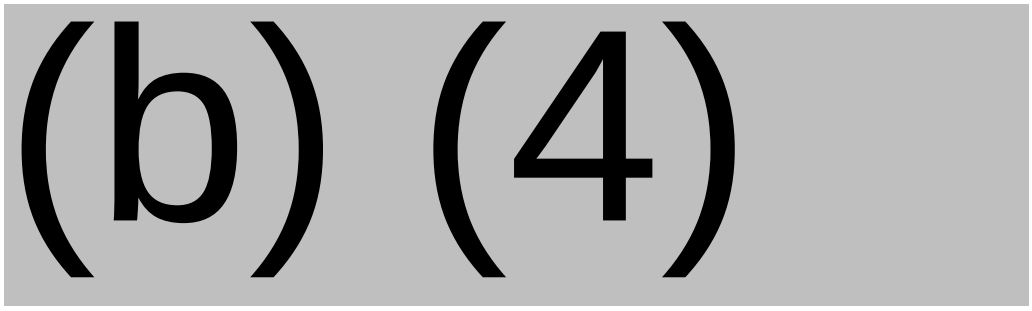
(b) (4)



(b) (4)

***Reviewer Comment**: Please see the process validation section of this review for supporting data of adequate product quality maintenance during this* (b) (4) *post-processing/pre-cryopreservation storage interval.*



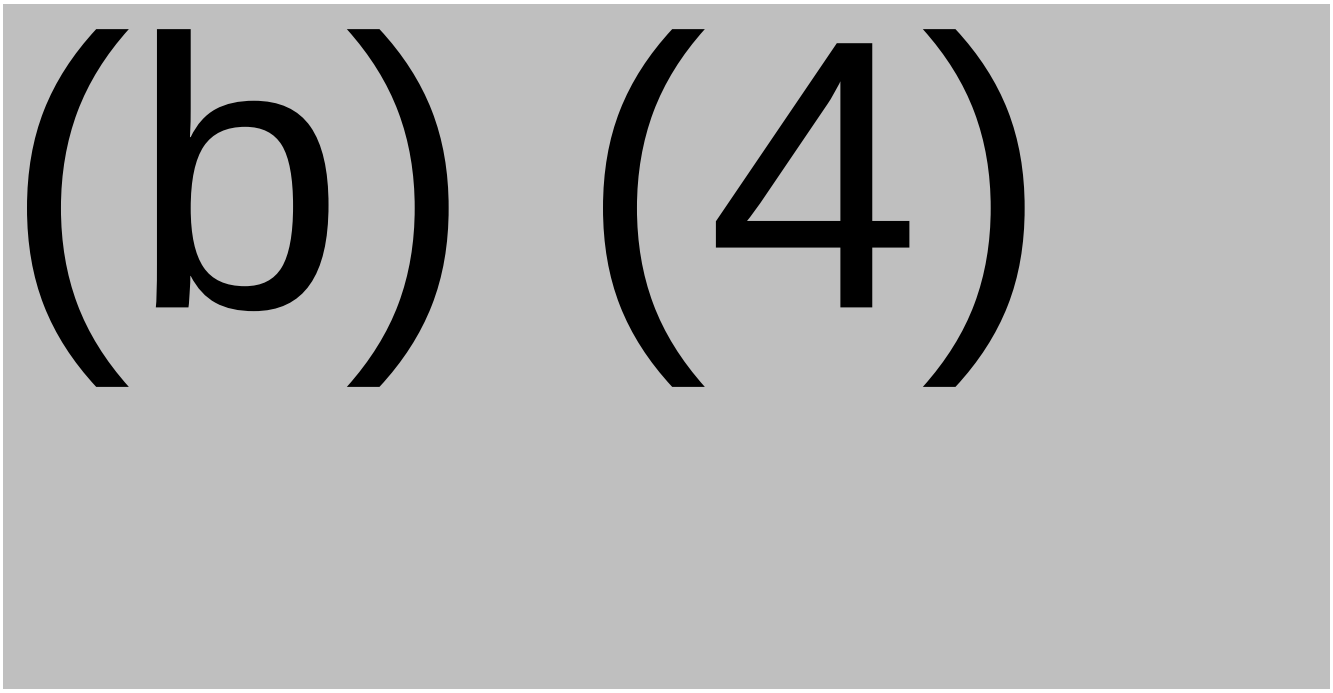


==========

CRYOPRESERVATION:

-(b) (4) **& Cryoprotectant Addition:**

The (b) (4) buffy coat/final product bag is prepared for cryopreservation by (b) (4)



[Figure 3, component B (Bloodworks Figure S.2.1-2 (b) (4) each segment separated by a (b) (4) Each segment is labeled with a traceability identifier; labels are verified by a second technologist and the verification is recorded on the processing Form (25-9-160). The Final Product bag and attached segments are removed from the (b) (4) and inserted into an overwrap bag (b) (4) which is sealed per SOPs CBP 9220 and CBP 5140, providing a fully enclosed final product package that offers a physical barrier from the environment.

- Control-Rate Freezing (CRF):
Units must be cryopreserved within 48 hours of collection. Final product cryopreservation is initiated in a (b) (4) cryopreservation device. CBUs are cooled to (b) (4) with a calculated freezing rate range of (b) (4) per SOP CBP 5040, "HPC(CB) Cryopreservation". Upon completion of the programmed freezing process, the CBU and representative samples are immediately transferred to the adjacent Quarantine LN2 storage (b) (4) .

***Reviewer comment**: During the 7/13/15 pre-license inspection a 483 observation was issued as the cryopreservation SOP and batch records didn't identify CRF product bag load range. The applicant revised SOP CBP 5040, "HPC, Cord Blood Cryopreservation and Storage" to include the load range of (b) (4) product bags in a CRF at a time. The applicant's response was acceptable (please see DMPQ review).*

- LN2 Storage (b) (4)
CBUs are continuously stored in (b) (4) freezers at ≤ -150°C while testing is being completed. The final product at time of release into inventory is taken from the Quarantine storage in a LN2 charged, temperature-monitored LN2 shipping containers to the permanent storage area on another floor and continues to be stored at ≤ -150°C after all release criteria are met. Bloodworks CBS uses (b) (4) HPC, Cord Blood unit storage. The (b) (4) temperature (b) (4) and the (b) (4) is typically between (b) (4) They are continually monitored by the automated computerized monitoring system, (b) (4) Monitoring System ((b) (4) The (b) (4) for these (b) (4) is at the highest possible placement in the (b) (4), monitoring the (b) (4) temperature ((b) (4)

***Reviewer comment**: During the 7/13/15 pre-license inspection a 483 observation was issued as qualification documents for the (b) (4) Monitoring System were not subjected to quality review per SOP QP 0563 Validation Protocol Development. The applicant responded by conducting and documenting retrospective review of the (b) (4) verification of the (b) (4) Monitoring System performed by the vendor and updated SOP QP 0563 to include instructions for QA/RA review to occur for vendor performed qualifications. The applicant's response was acceptable (please see DMPQ review).*

==========

THAWING & PREPARATION FOR ADMINISTRATION:

The CBUs are thawed per SOP CBP 7031, "Thawing a HPC, Cord Blood Unit".

• Prepare LMD/HSA Reconstitute Solutions #1 and #2:
Prior to use, visually inspect the 10% low molecular weight Dextran-40 (LMD) in saline for particulate matter; if crystallization is observed, do not use and discard appropriately. While working inside a biologic safety cabinet (BSC Class (b) (4)), aseptically and securely insert a sampling site coupler into one of the ports of a sterile 300 mL transfer bag labeled "LMD/25% HSA Solution #1", and add 5 parts (e.g. 25 mL) LMD and 1 part (e.g. 5 mL) 25% Human Serum Albumin (HSA), via syringe and needle. Prepare a minimum of (b) (4) as a volume equal to the HPC, Cord Blood product volume. Mix the LMD/HSA reconstitute solution by inversion and swirling the bag several times thoroughly without creating excessive bubbles, then store in a refrigerator to cool. Of note, on 1/5/16 the applicant stated they intend to update their draft PI label instruction (before approval) to pre-chill LMD/HSA solutions. A similar procedure is followed for Solution #2. A second sterile 300 mL transfer bag, labeled with "LMD/5% HSA Solution #2", is loaded with two times the HPC, Cord Blood unit volume using 1 part (e.g. (b) (4) LMD and 1 part (e.g. (b) (4) 5% Human Serum Albumin (HSA), mixed, and stored as above. Both LMD/HSA reconstitute solutions #1 and #2 must be used within 4 hours as manufacturer's package inserts for both 25% and 5% HSA include instructions to utilize no more than 4 hours after the container has been entered.

Reviewer comment: *Per SOP CBP 7031, "Thawing a HPC, Cord Blood Unit", LMD is inspected visually for particulate matter prior to use. If crystallization is observed, do not use and discard appropriately. The applicant should clarify why this note was not included in their 12/17/15 draft 'package insert'/'product information' (PI) label. On 1/5/16 the applicant communicated their intent to revise their draft PI label to include visual inspection for particulate matter prior to use. On 1/22/16 the applicant's final revised PI label's "Instructions for Preparation for Infusion" section included visual inspection of LMD solution for particulate matter prior to use and if crystallization is observed, to not use and discard appropriately. The applicant's revision is acceptable.*

Reviewer comment: *The BLA submission Table S.2.5.1-8 (Process Validation – Final Product Thaw) indicates LMD/HSA solution is stored in a refrigerator to cool. However, the revised (12/17/15) draft package insert (PI) label instructions don't appear to require use of pre-chilled LMD and HSA. On 1/5/16 the applicant communicated their plan to revise their draft PI label to pre-chill LMD/HSA solutions to accurately reflect their validation practice, and FDA has added that in our draft revisions. On 1/22/16 the applicant's final revised PI label's "Instructions for Preparation for Infusion" section stated to pre-cool the LMD, 25% and 5% HSA Solutions in the refrigerator. The applicant's revision is acceptable.*

• Removal from Storage:

After removing the cryobag from LN2 storage, the cryobag is removed from the canister. The unit ID number on the cryobag is confirmed to match the unit ID number on the physician's orders and all applicable paperwork. The cryobag is quickly inspected for visible tears, breaks or cracks in the overwrap, freezing bag (cryobag), ports, segments, or seals. If visible tears, breaks, or cracks are observed, the cryobag should be replaced into storage ≤ -150°C and the Medical Director consulted before proceeding. Using scissors that have been wiped down with (b) (4) alcohol (b) (4), remove overwrap, any segments are detached, and segments are replaced in ≤ -150°C storage until needed.

- (1 of 2) Thaw-Dilute (No Wash):

• Thawing the HPC, Cord Blood:
The HPC, Cord Blood product cryobag is placed inside a large re-closable plastic bag and sealed closed. The water bath temperature is confirmed to be 37°C ± 2°C and the bag is immersed completely in the water bath. The cryobag is gently agitated and kneaded until the product reaches a slushy liquid consistency. The cryobag is then removed from the water bath and removed from the reclosable bag. The cryobag integrity is quickly inspected for tears and leaks. If visible cracks or breaks are observed, the Medical Director is consulted before proceeding.

• Transfer the HPC, Cord Blood (in the Biologic Safety Cabinet, BSC):
The thawed cryobag is transferred into a BSC where the cryobag and port covers are wiped down with (b) (4). The port covers are cut off with scissors (that have been wiped and disinfected with (b) (4)) cutting only through the outer layer of plastic and not the inner port column. Using aseptic technique, a sampling site coupler is inserted into each port. Using a 30 mL syringe with a 14 gauge needle, the contents from both compartments are aseptically withdrawn into the syringe. The HPC, Cord Blood unit volume (~25 mL) is measured via syringe, recorded, and then the product is slowly and aseptically transferred using the inserted sampling site coupler into a second sterile 300 mL transfer bag with "Thawed Final Product". The HPC, Cord Blood unit cryobag is placed on an ice bath or refrigerated gel packs in the BSC.

• HPC, Cord Blood Dilution:
The LMD/25% HSA Solution #1 bag is removed from the (b) (4) refrigerator and placed in the BSC. Working inside the BSC, a 60 mL syringe with a 14 gauge needle is aseptically filled with a volume of the pre-chilled LMD/HSA solution (e.g. 25 mL) equal to the HPC, Cord Blood unit volume (e.g. 25 mL). Aseptically attach the 60 mL syringe containing LMD/HSA Solution #1 to the 300 ml transfer bag containing the thawed product.

LMD/HSA Solution #1 is slowly added to the thawed HPC, Cord Blood product while mixing the bag. During addition, the syringe and cryobag are maintained chilled on ice or refrigerated gel packs. Rest the HPC, Cord Blood product bag for 5 minutes and maintain the bag chilled on ice or refrigerated gel packs. The LMD/5% HSA Solution #2 bag is added in a similar way, but adding two times (e.g. 50 mL) of the original volume of the HPC, Cord Blood unit (e.g. 25 mL).

The attached syringe and HPC, Cord Blood product bag are maintained chilled on ice or refrigerated gel packs.

Reviewer comment: *During their proposed dilution, it appears there would be a minimum volume of 100ml in the transfer bag by step 4 "Measure and Sample" and it is not clear how this size volume can be measured with one 60ml syringe that is attached to the bag. On 1/5/16, the applicant communicated their plan to revise their draft PI label to calculate the final volume in place of measurement, and we have this flagged in the FDA revision of 'Instructions for Preparation for Infusion' for the applicant to address this. On 1/22/16 the applicant's final revised PI label's "Instructions for Preparation for Infusion" section included calculation of final volume in place of syringe measurement. The applicant's revision is acceptable.*

• HPC, Cord Blood Measure and Sample:
Within the BSC, sample volumes are aseptically removed, using the attached syringe, for quality control tests, such as nucleated cell counts (b) (4) viability (b) (4) CD34+ analysis (b) (4), and sterility testing (b) (4) Subtracting the sampled volume equals the infusion volume.

• HPC, Cord Blood Infusion:
The product is infused as soon as possible using a (b) (4) micron blood component recipient set. The product expiration time is 4 hours from the time of thaw.

Reviewer comment: *Of note, BLA submission section 3.2.P.5.2.7 "Thawing and Preparation for Administration" states "the product expiration time is 4 hours from the time of thaw". Also, the 12/17/15 draft PI label's section (IV. PROCEDURE/#4 Measure and sample) states: "Note: The recommended use time of thawed HPC, Cord Blood product is 4 hours from the time of thaw." While the applicant indicated on 1/5/16 plans to revise BLA section 3.2.P.5.2.7 and their proposed draft PI label to state, "Infuse product as soon as possible", after subsequent discussion with the applicant, they communicated on 1/8/16 that they will revise their draft PI label to match the 4 hour expiration in section 3.2.P.5.2.7. On 1/22/16 the applicant's final revised PI label's section 2.2 and the "Instructions for Preparation for Infusion" section contained language recommending an HPC, Cord Blood product expiration time of 4 hours from the time of thaw, if stored at 2-8°C. The applicant's revisions are acceptable.*

- (2 of 2) Thaw-Dilute-Wash:

• HPC, Cord Blood DMSO and Volume Reduction (Thaw-Wash):

Background:
While the applicant's draft 'package insert'/'product information' (PI) label included "Instructions for Preparation for Infusion" for a 'thaw-dilute' method, it did not include a 'thaw-wash-dilute' method per their concerns of potential risk of a wash procedure on thawed CBU quality. On 12/3/15 the OCTGT Cord Blood CMC Working Group decided that Bloodworks

should revise their draft PI label to include a post-thaw cryoprotectant removal/reduction method, for use in transplant centers that perform this step. On 12/17/15, the applicant provided a revised draft PI label that included the following a thaw-wash/DMSO reduction method per SOP CBP 7033, 'DMSO Removal & Volume Reduction of an HPC, Cord Blood Unit'.

Under their 12/17/15 draft PI label's "Product Receipt" section, they have a "NOTE" that if the patient is small, the volume of the final product will need to be reduced by centrifugation and removal of supernatant to a volume recommended by the transplant physician caring for the patient. The applicant stated that if the patient weighs 2.5 kg or less, the centrifugation and supernatant removal will be required for HPC, Cord Blood units to reduce DMSO as well as overall volume of the unit.

Reviewer comment: *This "NOTE" should be moved from the draft PI label's "Product Receipt" section to the "Preparation" section. On 1/22/16 the applicant's final revised PI label's section 2.2 and "Instructions for Preparation for Infusion" section (i.e. III. Preparation and IV. Procedure) contained considerations of recipient's weight, possible fluid restrictions, and a recommended limit on DMSO administration (>1 g/kg body weight). The applicant's revisions are acceptable.*

The thawed, diluted product bag is centrifuged at 400 x g for 20 minutes at 4°C. A 300 ml transfer bag is sterile connected to the product bag. The product bag can remain in the centrifuge cup during docking to ensure the cell pellet is not disturbed. The empty 300 ml transfer bag is put on a scale, then tare the scale. The HPC, Cord Blood product bag is placed in a plasma extractor. Using the plasma extractor, the supernatant is pressed off until ~20 mL cell pellet remains. The cell pellet is resuspended and the concentrated product is volumetrically measured. In a Biosafety Cabinet, add supernatant to reach a total volume of 20 mL.
Document the final infusion volume and infuse product as soon as possible.
Note: The recommended use time of thawed HPC, Cord Blood product is 4 hours from the time of thaw.

Reviewer comment: *On 1/5/16, the applicant communicated that the bag with the sampling site inserted can be centrifuged, that the tubing does need to be clamped, and that they intend to revise their draft PI label to include clamps and centrifuge to the "Material" section. Additionally, instructions given in the PI label should be clear about how the bag and tubing should be placed in the centrifuge and this should be communicated to the applicant during the PI label review/negotiating phase. On 1/22/16 the applicant's final revised PI label's "Instructions for Preparation for Infusion" section included clarifications to this procedure that were found to be acceptable.*

PROCESS VALIDATION

Cord Blood Processing Validation:

The applicant performed a prospective 'process and materials validation' to demonstrate that the laboratory processes and materials for HPC, Cord Blood processing by the (b) (4) will consistently produce acceptable post-processing results that meet the specifications defined by the Cord Blood Services department and are consistent with "Table A. Required and Recommended Tests and Test Results" of FDA's March 2014 finalized Guidance document. Their process validation required availability of at least (b) (4) The applicant indicates this validation was reviewed and approved by their Cord Blood Services QA/RA Department to proceed prior to execution.

(b) (4)

(b) (4)

(b) (4)

[redacted]

(b) (4)

[redacted]

(b) (4)

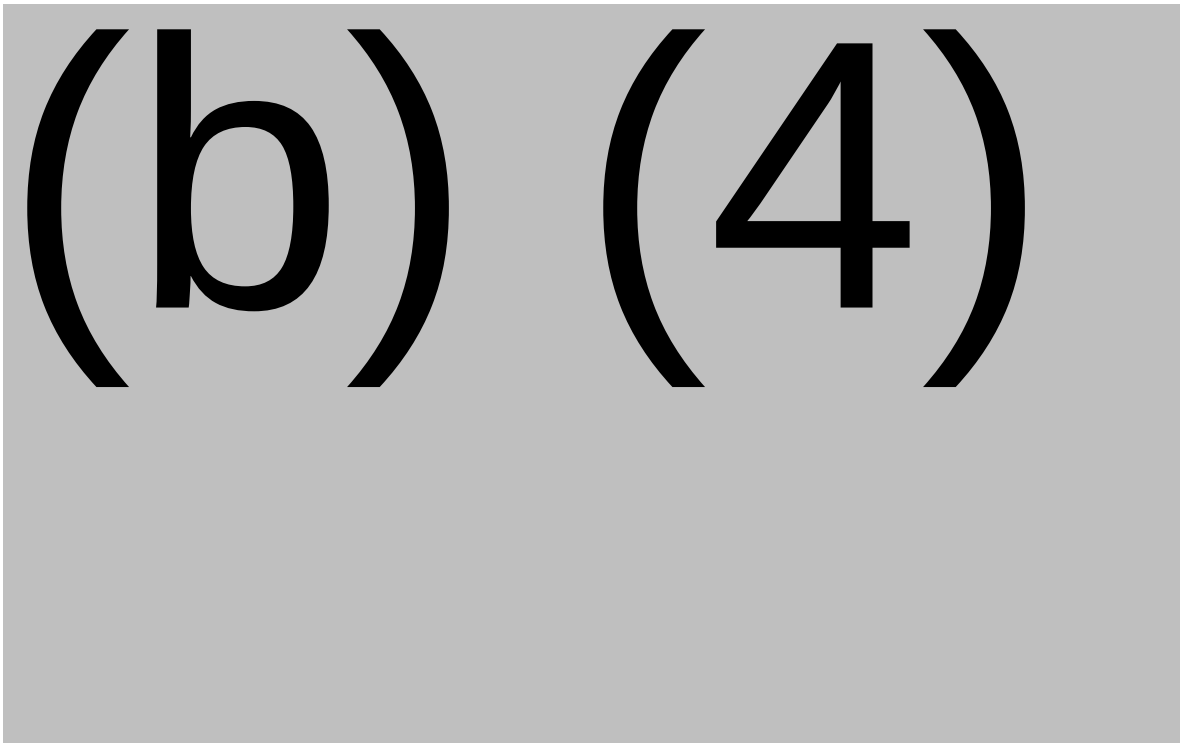
[redacted]

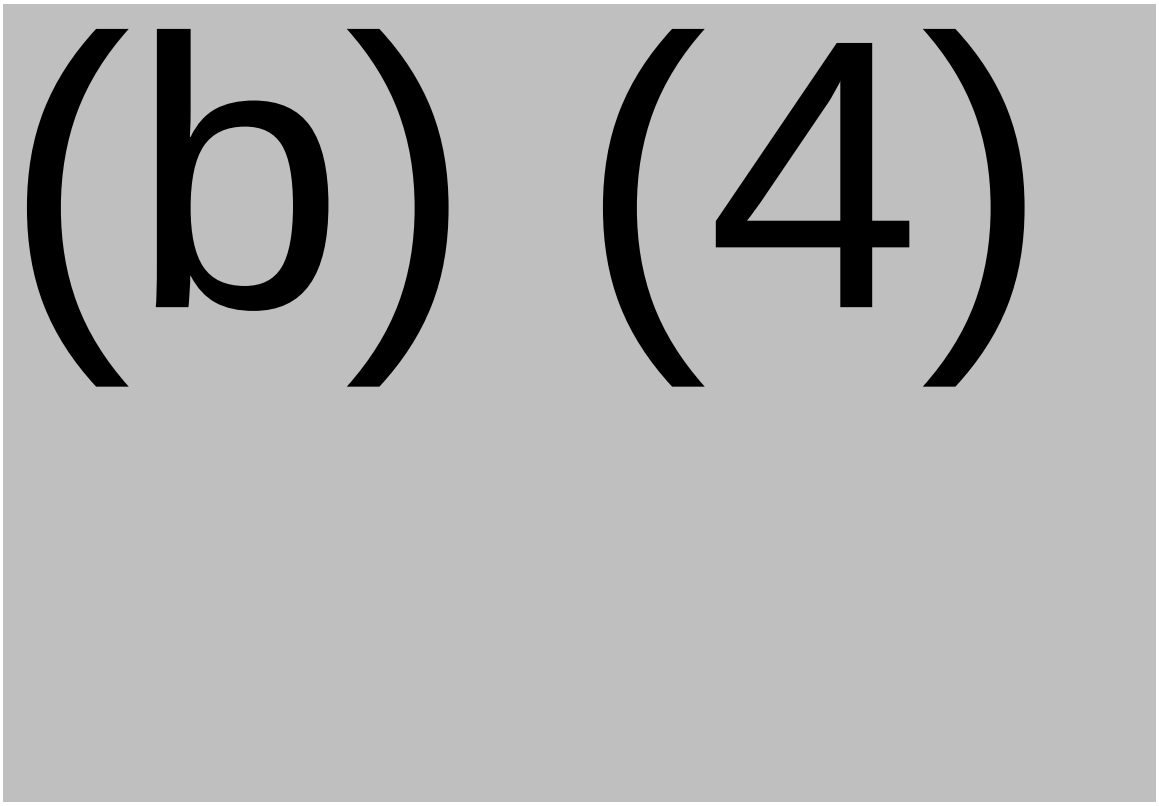
(b) (4)

[redacted]

(b) (4)

(b) (4)





(b) (4)

Analytical Results of Three Consecutive HPC, Cord Blood Unit Batches:

Batch records for three consecutive, separate HPC, Cord Blood units were submitted to demonstrate consistency in their manufacturing.

TABLE 13. Analytical Results of Three Consecuti

Parameter	Specification	(b) (4)		
Collection Volume				
Birth; Collection; Processing Dates	Report			
Collection Location	Report			
Safety:				
Infectious disease testing (1 of 2)	Negative: HIV NAT, HBV NAT, HCV NAT, WNV NAT			
Infectious disease testing (2 of 2)	Non-Reactive: HBsAg, a-HIV-1/2, a-HBc, a-HTLV-I/II, a-HCV, STS, CHAG,			
Sterility cultures	No growth			
Hemoglobin	No homozygous hemoglobinopathy			
Purity & Potency:				
Total nucleated cells (TNC)	≥ $5x10^8$ TNC per CBU pre-freeze			
(b) (4)				
Viability	≥ 85% viable nucleated cells pre-freeze			
Viable CD34+ cells	≥ $1.25x10^6$ viable CD34+ cells/CBU pre-freeze			
(b) (4)	(b) (4)			
Identity:				
HLA typing	Report; Confirm	(b) (4)		
Blood Group & Rh Type	Report			
Processing:				
(b) (4)				

(b) (4)

Reviewer comment: *Information submitted demonstrates consistent manufacture of three consecutive HPC, Cord Blood units that met intended product characteristics.*

Stability Testing, Evaluation & Protocol:

The applicant's stability testing (BLA section 3.2.P.8.1) of HPC, Cord Blood units is intended to ensure that storage conditions maintain the HPC, Cord Blood units' (prepared by the (b) (4) method) integrity, functionality, quality and suitability for transplant.

The (b) (4) method was implemented as standard practice on 2/27/12. Stability testing was performed to support a (b) (4) initial expiry per data from (b) (4) units taken from (b) (4) of calendar (b) (4) CBU inventory that were tested for TNC recovery, viability, packaging integrity, & sterility. After licensure the applicant will continue (b) (4) assessment of at least (b) (4) processed units (b) (4), per SOP CBP 8090 "Evaluation of Product Stability", with the goal of (b) (4)

Per SOP CBP 6160 "Product Stability (Quality Assessment)", (b) (4) random representative (b) (4) processed units were selected per statistical analysis and tested. The units designated and available for testing were randomized by selection as described in their SOP. Units were required to meet minimum post-processing acceptance criteria for TNC, CD34, viability, Colony Forming Assay (CFA), and negative microbiological culture results. Units were retrieved from their long-term storage (at ≤ -150°C in the LN2 freezer). Each unit was then evaluated for product integrity and tested as described in SOP CBP 6160 "Product Stability (Quality Assessment)".

The post-thaw method of preparation for infusion used a method employing dilution of the thawed CBU with a slightly (b) (4) Dextran 40 and human serum albumin. The applicant states this method has been shown to preserve viability, functionality, and engraftment potential of cord blood cells post-thaw and cites published references by Laroche, et al. (Transfusion; 45:1909-1916. 2005), Rubinstein et al. (PNAS USA; 92: 10119-10122, 1995), Regan et al. (Transfusion; 50:2670-2675; 2010) & Barker et al. (Biol Blood Marrow Transplant; 15:1596-1602; 2009).

The applicant states each CBU was visually inspected for bag and label integrity & the product bag was inspected for cracks and/or an incomplete seal. The units were thawed using the dilution method per SOP CBP 7031 "Thawing an HPC, Cord Blood Unit". Samples were aseptically removed & the following tests were performed on the samples:

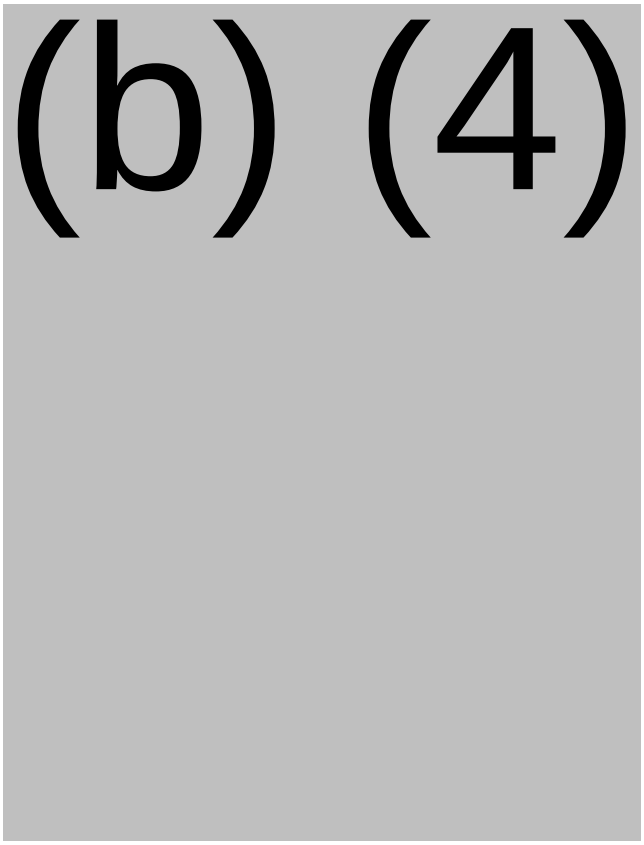
• Cell count

• Viability testing
• CD34+ testing
• CFU/CFA
• Aerobic & anaerobic microbiology testing

Results (recorded on their 25-9-097 "Product Quality Assessment Summary" Form) included % TNC Recovery/%MNC Recovery, % Viability, and % Viable CD34 Recovery.

Stability TNC % Recovery Results:

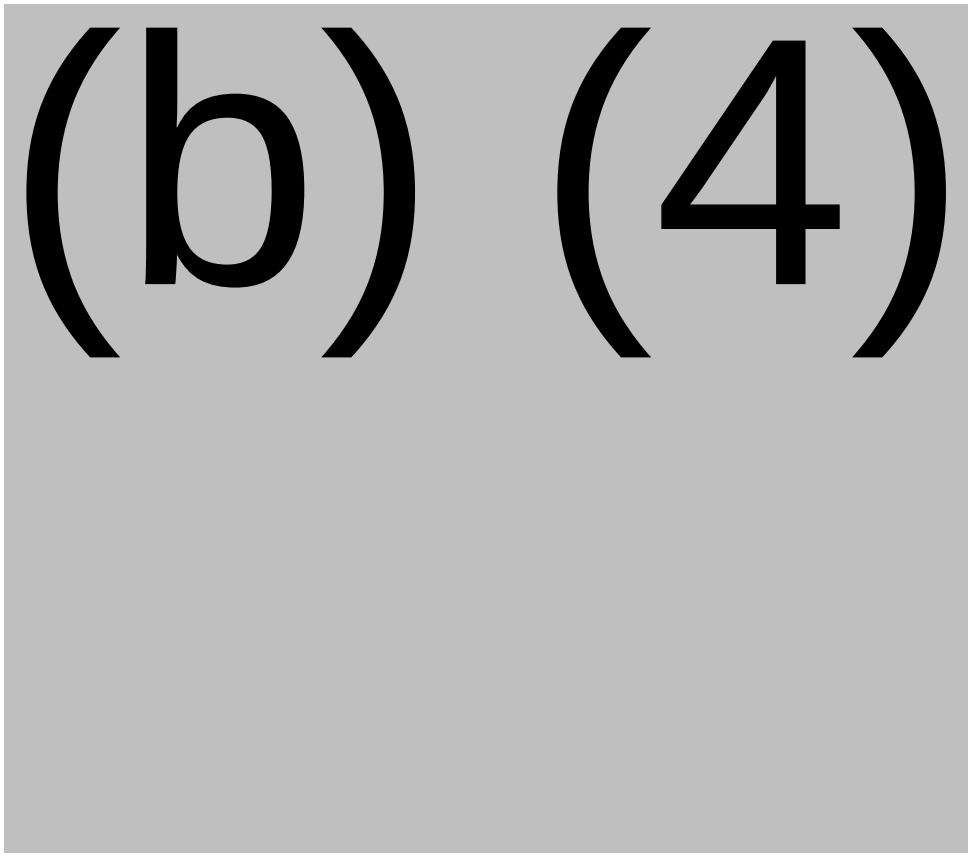
Recovery of TNC showed a mean of (b) (4), with a range of (b) (4). The applicant states that in published studies of cord blood unit processing and in comparison of the pre and post-thaw values by Laroche et al., Regan et al., and Rubinstein et al., these results are typical and expected.



Reviewer comment: *Test results met predefined acceptance level of* (b) (4) *TNC recovery post-thaw.*

Stability Cell Viability Results:

The applicant's viability of the recovered nucleated cells saw more variability (mean of (b) (4) with a range of (b) (4) The applicant states that recovery of mononuclear cells (MNCs) post-thaw is typically (b) (4) if they are frozen and thawed using acceptable techniques; however, as CBUs are whole blood, they containing granulocytes. The applicant's data shows the (b) (4) had recoveries of mean of (b) (4). The applicant states that mature granulocytes are known not to survive thaw post cryopreservation & that less mature granulocytes may survive. The % of granulocytes in each CBU was recorded (typically (b) (4) The applicant states that granulocytes lower the viability values of whole blood in post thaw cell preparations but are not relevant to the effectiveness of the graft as mature granulocytes to not contribute to engraftment. The applicant states that both immature hematopoietic stem cells and mature lymphocytes tend to survive cryopreservation well and do contribute to engraftment. The applicant cites published data on post-thaw viability, i.e. Rubinstein & colleagues reported post-thaw viability of whole cord blood at a mean of 62% & Laroche et al. reported mean viability of 62% (b) (4) method (same as was used here).

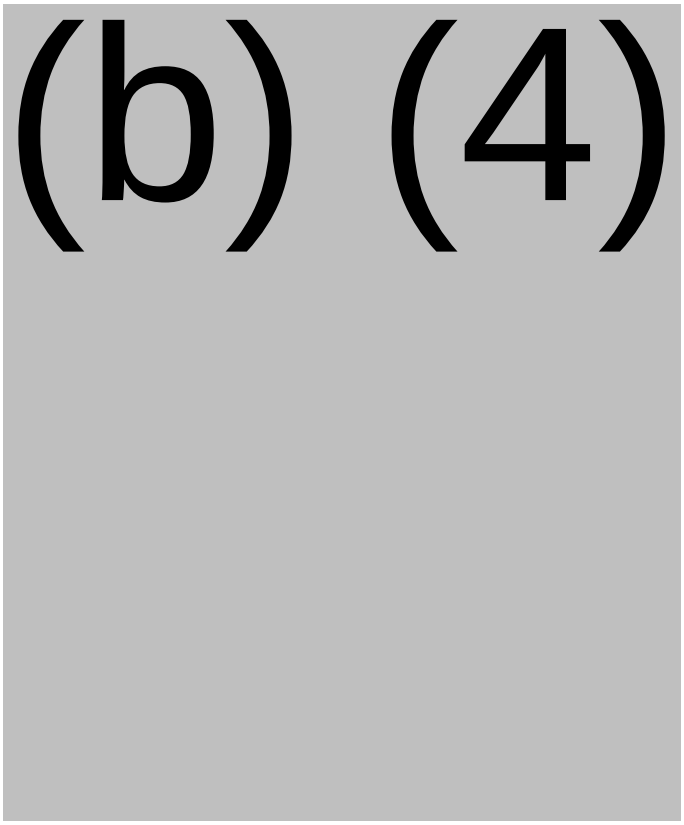


Reviewer comment: *Test results met predefined acceptance level of 100% of the CBUs meet (b) (4) nucleated cell viability post-thaw by (b) (4).*

Stability Viable CD34+ Count Results:

The applicant states their CD34+ cell recovery showed a mean of (b) (4) (range of (b) (4) recovery. The applicant states their method measures only viable CD34+ cells so the losses of

expected cell recovery attrition and viability are combined in the result reported. Their statistical plan was all samples should have a recovery of (b) (4) with an expected mean of (b) (4). The applicant states their results are consistent with the cited findings of St. Louis Cord Blood Bank in their published series (Regan et al.) using the same CD34+ analysis method.

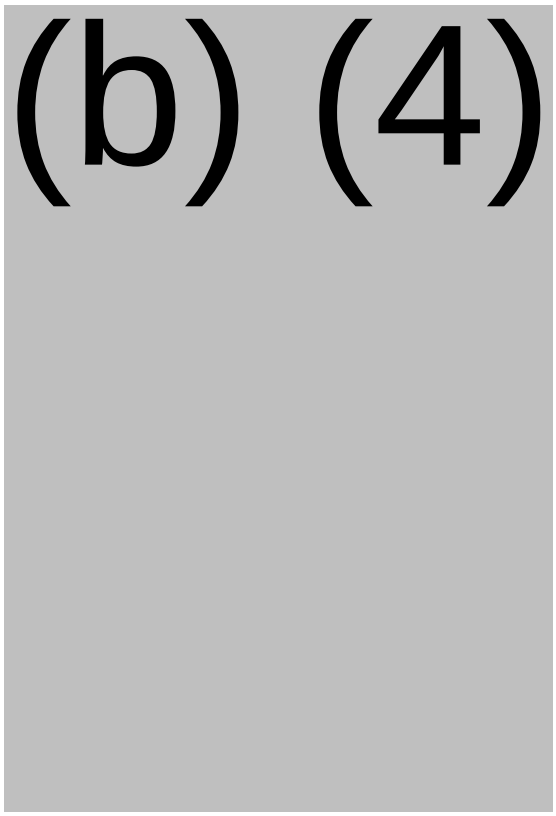


Reviewer comment: *Test results met predefined acceptance level of 100% of the CBUs meet (b) (4) CD34+ recovery post-thaw.*

Stability Colony Forming Units (CFU)/Colony Forming Assay (CFA) Results:

The applicant states that the colony forming assays (CFA) produced growth in all post-thaw units with a mean of (b) (4) of tested units. The applicant states this test is notoriously variable in laboratory testing situations & that their criterion was that all units would produce colonies. The applicant cites St. Louis Cord Blood Bank's published data (Regan et al.) that reported a mean of 75% recovery of colony growth and another report of 64% mean recovery of CFAs (Laroche et al.).

TABLE 17. Stability CFU/CFA Results



Reviewer comment: *Test results met predefined acceptance level of 100% CFU growth.*

Stability Sterility Results:

The applicant's limit was 100% negative sterility cultures (in-house (b) (4) method) for both the post-processing and thaw samples.

Reviewer comment: *Test results met predefined acceptance level of 100% negative for sterility and all units showing acceptable labeling and container integrity (i.e. intact overwrap, freezing bag, segments, seals & ports, & legible bag and segment labels).*

Cryopreservation Validation:

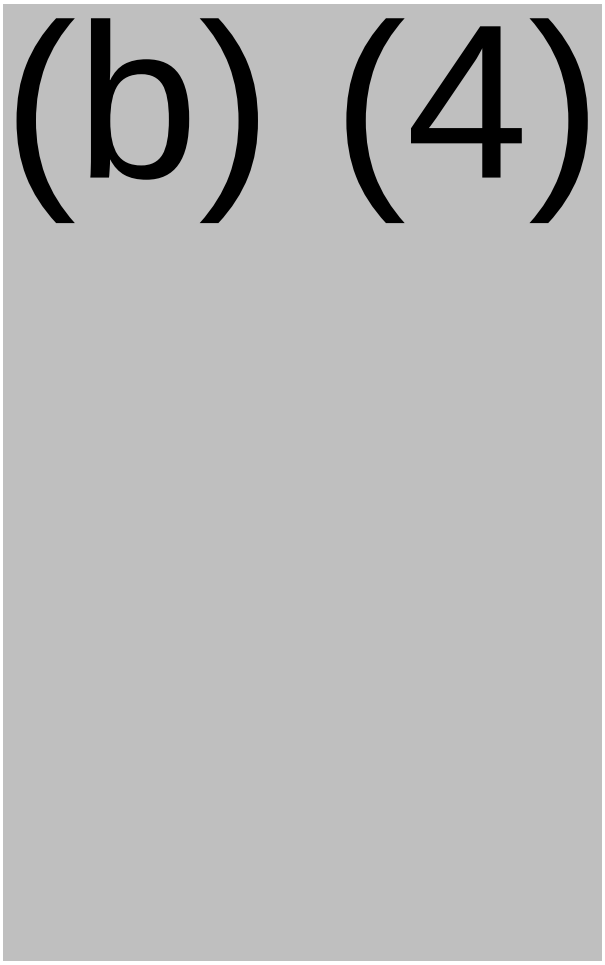
The applicant performed a prospective 'process and materials validation' to demonstrate that the laboratory processes and materials for HPC, Cord Blood cryopreservation will consistently produce acceptable results regarding physical integrity for intact final product packaging, and intact and legible labeling that meet the specifications defined by the Cord Blood Services department. Their cryopreservation validation included (b) (4) . The applicant indicates this validation was reviewed and approved by their Cord Blood Services QA/RA Department to proceed prior to execution.

(b) (4)

(b) (4)

(b) (4)

TABLE 19. Controlled-Rate Freezer Validation



(b) (4)

(b) (4)

Reviewer comment: *The LN2 storage conditions met the applicant's criteria.*

• Cryobag, Overwrap, & Bag Label Acceptability:

(b) (4)

Reviewer comment: *The applicant's criteria were met as all* (b) (4) *final product bags and overwraps were intact and all freezing bag and segment labels were intact and legible upon inspection.*

==========

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

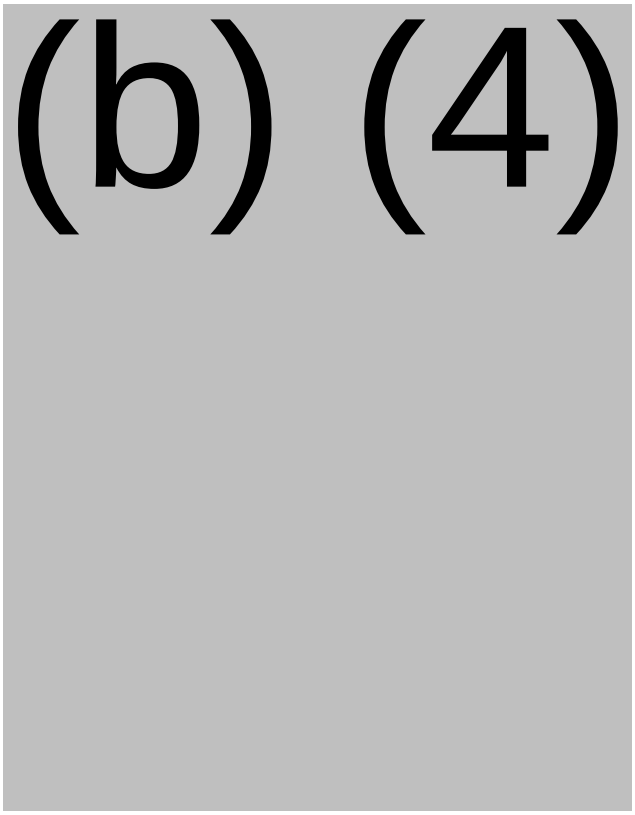
Reviewer comment: *Test results met predefined acceptance level of* (b) (4) *post-thaw.*

(b) (4) :

(b) (4)

:

(b) (4)



(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer comment: *Test results met predefined acceptance level of* (b) (4) *post-thaw by* (b) (4) *.*

(b) (4)

(b) (4)

(b) (4)

Reviewer comment: *Test results met predefined acceptance level of* (b) (4) *post-thaw.*

(b) (4)

Reviewer comment: *Test results met predefined acceptance level of* (b) (4) *for* (b) (4) *post-thaw.*

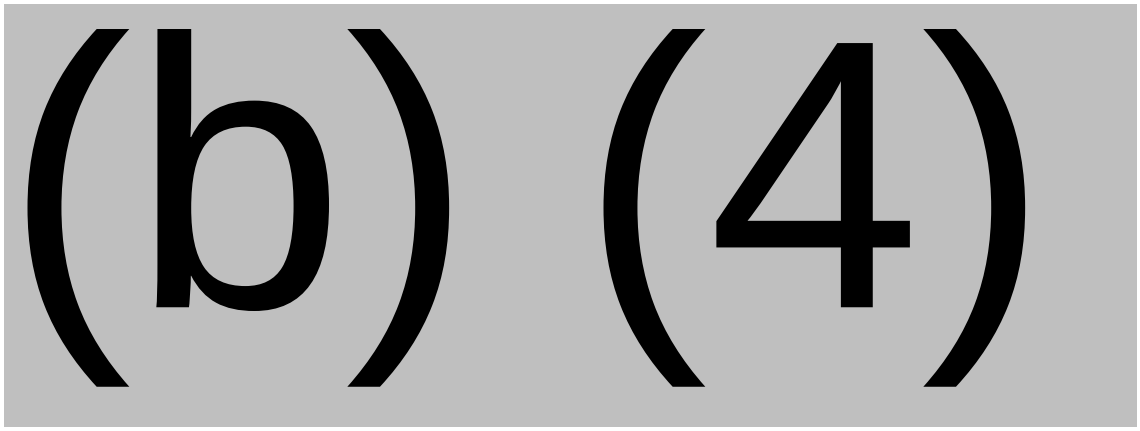
(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)



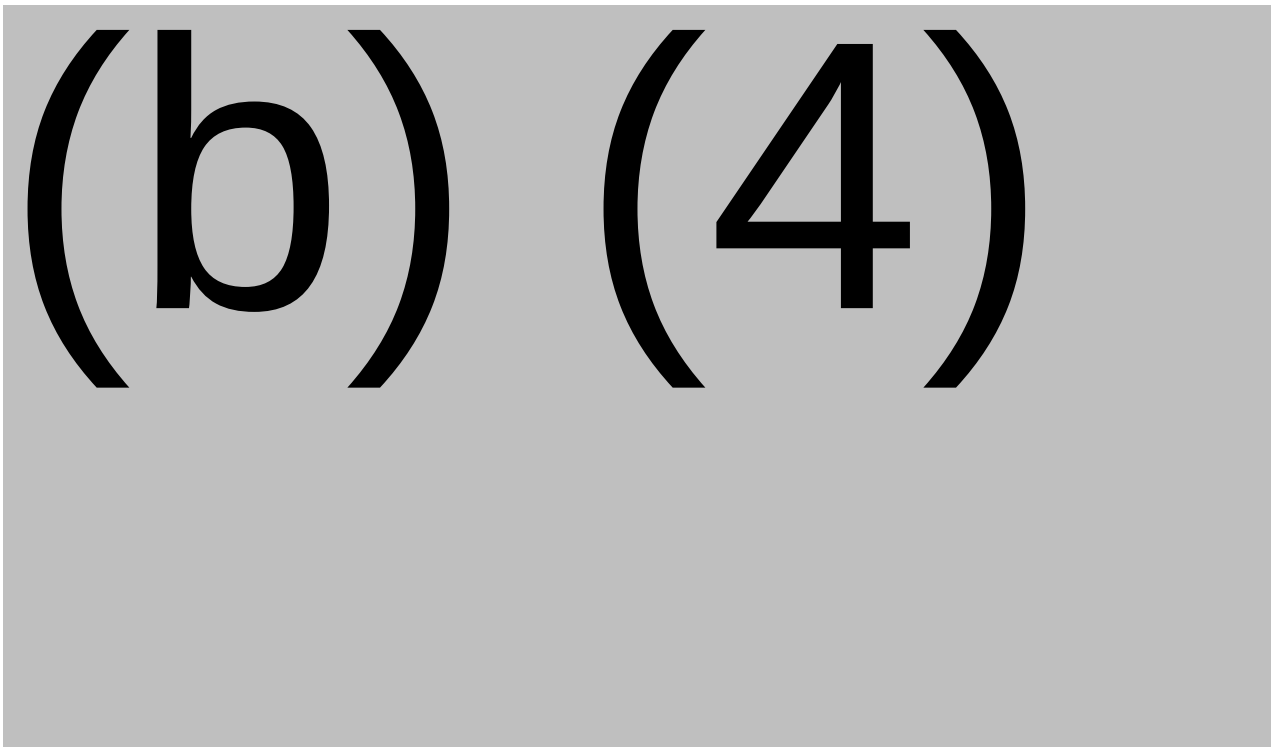
(b) (4)

(b) (4)

(b) (4)

.

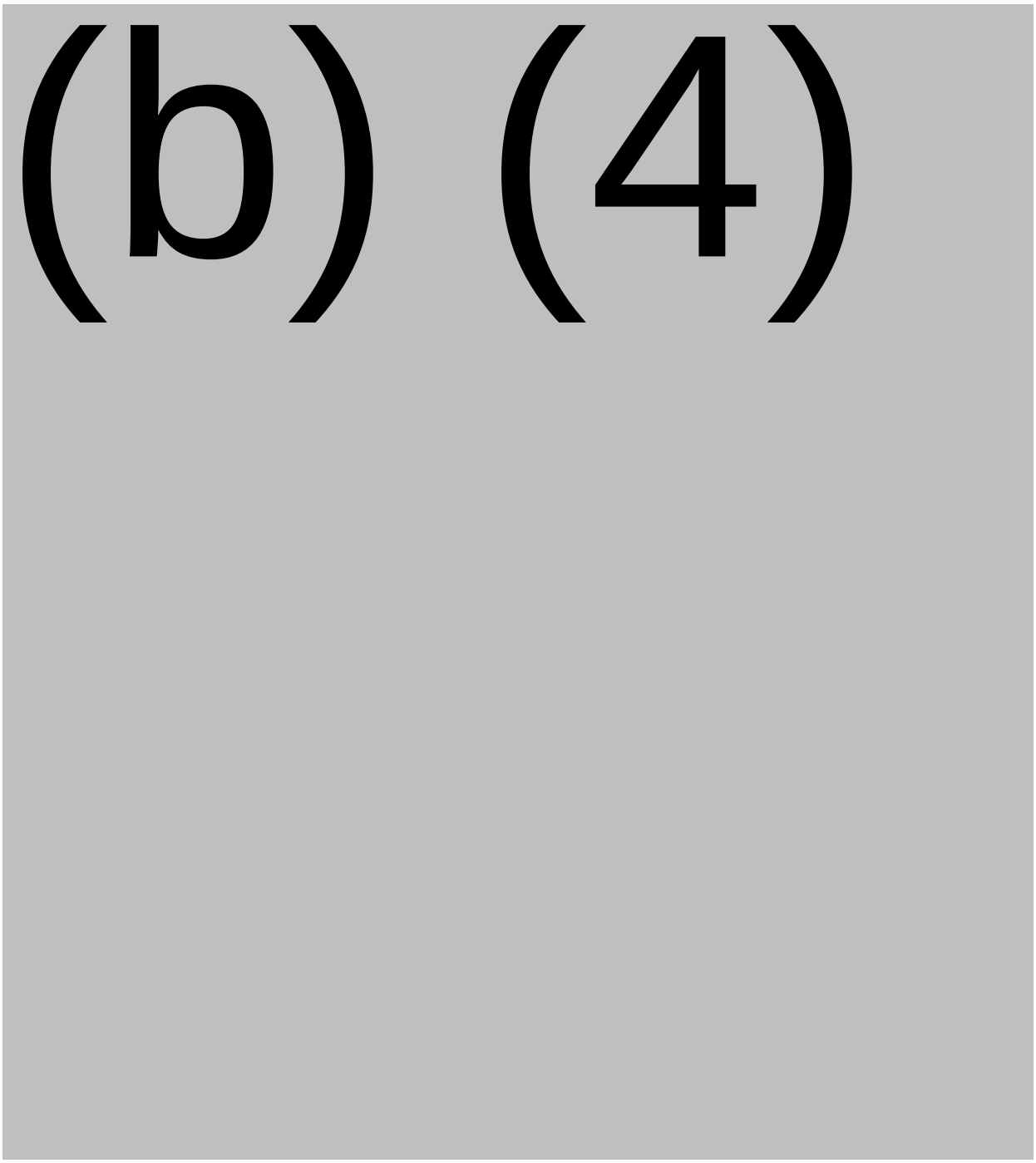
(b) (4)



(b) (4)

(b) (4)

(b) (4)

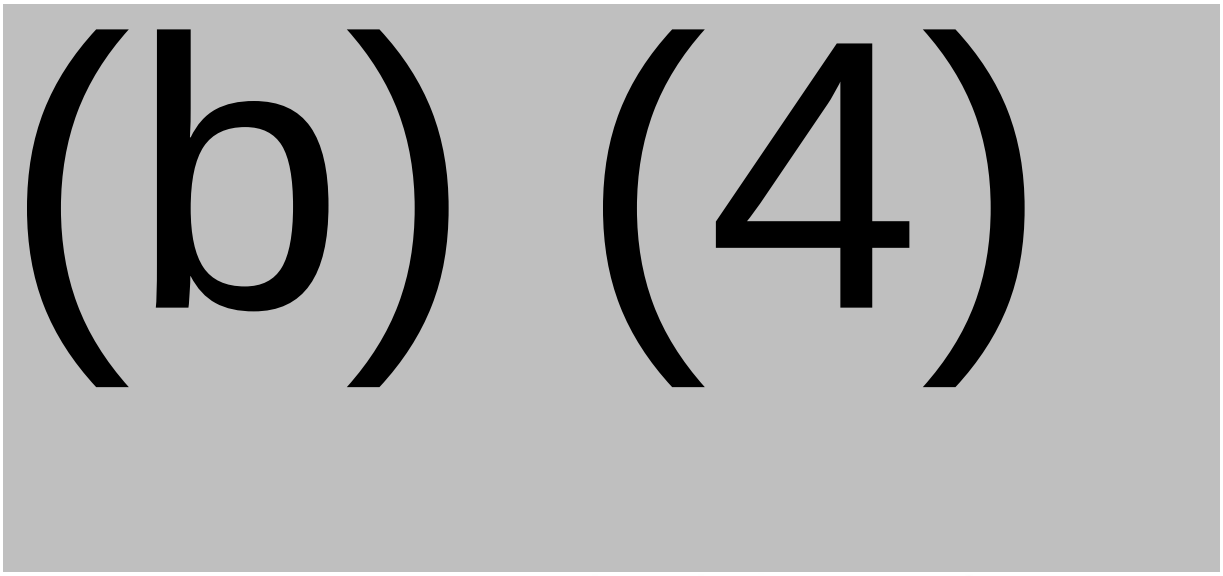


(b) (4)

(b) (4)

==========

(b) (4)



==========

Emergency Product Recovery:

The applicant states that each unit is inspected for integrity before shipment; however, events during shipment or handling at the transplant center may result in breakage. The transplant physician, receiving local laboratory director, and Bloodworks Cord Blood Services should be notified immediately if the HPC, Cord Blood unit bag appears to be fractured or compromised by a broken-off segment. If the only choice for transplant is to use a CBU with a possible container failure, a procedure for product recovery is included in the package insert. If product integrity has been compromised but the transplant center physician decides that this product is to be used for the intended patient, a culture of the thawed contents is recommended to give information to the clinical team about possible contaminants and their antibiotic sensitivities in case the patient requires antibiotic treatment for this organism/these organisms.

The applicant's instructions include:

1. Handling the cryobag with extreme caution when removing it from LN2, metal cassette, and protective overwrap and during the thaw procedure as cryobags can be very fragile. This is applicable both during inspection of the product upon arrival and during the thawing process.

2. Wiping the external surface of the cryobag with isopropyl alcohol before the cryobag is placed inside a sterile zip-lock bag. This process is intended to position the thawing laboratory to potentially recover the product in the case of an unexpected leak or container failure during thawing or centrifugation.

3. Notification of the Bloodworks CBS department and the transplant physician/team and local laboratory director immediately if any portion of the product or container seems to be damaged or compromised. If the bag is compromised, further handling is moved into a biological safety cabinet after thawing.

4. The transplant physician (or designee) is responsible to determine whether the product will be used or discarded if the container is compromised at any step of the procedure. If the product is accepted for use, recovery of the product may be attempted as described below.

    a. Using a long (3-5 inch) blunt needle (a sterile spinal needle with trochar removed, if available).
    b. Attaching the blunt needle to a sterile 60 mL syringe.
    c. Aspirating the product and injecting it into a sterile transfer bag
    d. Completing processing of the transferred product as indicated.
    e. Performing sterility testing on the product sample after final processing.
    f. Alerting the clinical team at the transplant center that the product was exposed and could be contaminated.

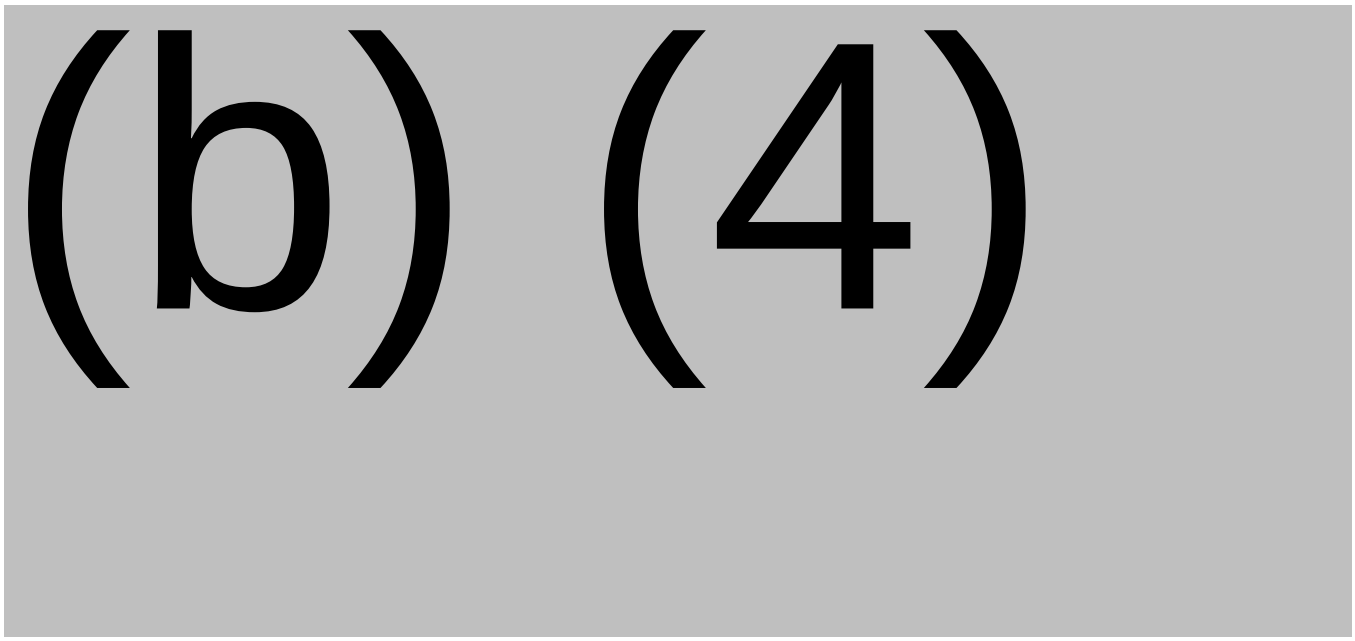
5. Further investigation as to the cause of the container failure may be warranted. If the unit is not used for transplant, return of the damaged unit may be requested. The Laboratory Director at Bloodworks Cord Blood Services Lab will provide instructions.

Reviewer comment:
The emergency recovery procedure appears to be adequate.

Sterility Testing & Validation

Proposed Sterility Test Procedure and Lot-release Specification

Bloodworks has proposed to perform the Sterility Test (for lot release) for HPC, Cord Blood using the following instrument, media and conditions:



Reviewer comments:

1. *The* (b) (4) *system is a well-known* (b) (4) *and has been used for the Sterility test of other products reviewed by this office. The composition of the* (b) (4) *is available on the* (b) (4) *website and the information is adequate.*
2. *The proposed* (b) (4) *test sample* (b) (4) *) is a process by-product consisting of* (b) (4) *. The applicant is proposing* (b) (4) *HPC, Cord Blood product volume is very* (b) (4) *and all of it is needed for a successful transplant in the recipient.*

   Based on the above facts and the:
   - *functionally closed nature of the processing method,*
   - *total volume of the by-product RBC and plasma fractions* (b) (4)
   - *same time of origin for product and by-product fractions, and*
   - *results of the method suitability (bacteriostasis/fungistasis) testing (described below),*

   we agree that the proposed test sample is an appropriate alternative to use for the Sterility Test of "HPC, Cord Blood" manufactured by Bloodworks.

Method Validation:

The applicant is using an alternative qualitative method for the Sterility Test but did not provide actual validation data for method specificity, limit of detection, ruggedness and robustness of the (b) (4) system using (b) (4) in their BLA.

Reviewer comments: *Although the applicant did not submit actual method validation data in the BLA, it is acceptable in this case due to the following reasons (Note: As FDA currently does not have a published guidance on the validation of Alternate Microbiological Methods, we followed the recommendations of the revised USP (b) (4) published in 2015, and (b) (4) published in 2013):*

1. *From our prior experience (based on the data from published scientific literature and regulatory documents submitted by (b) (4) to our office) with the (b) (4) and the above (b) (4) we know that this system/media combination has adequate levels of specificity (able to detect a very broad range of microorganisms), limits of detection (able to detect (b) (colony forming unit), ruggedness (similar degree of precision of test results obtained by different analysts and from different media lots) and robustness (the system remains unaffected by deliberate variation of ambient temperature).*
2. *The applicant's instrument has installation and operational qualifications as per the manufacturer's specification (reference: page 3 of 3.2.S.4.3.2.2 (b) (4) Validation Addendum.pdf of STN 125585/0/2).*
3. *The method suitability data provided additional assurance on method validation as described below.*

Method Suitability:

The method suitability studies were done using:

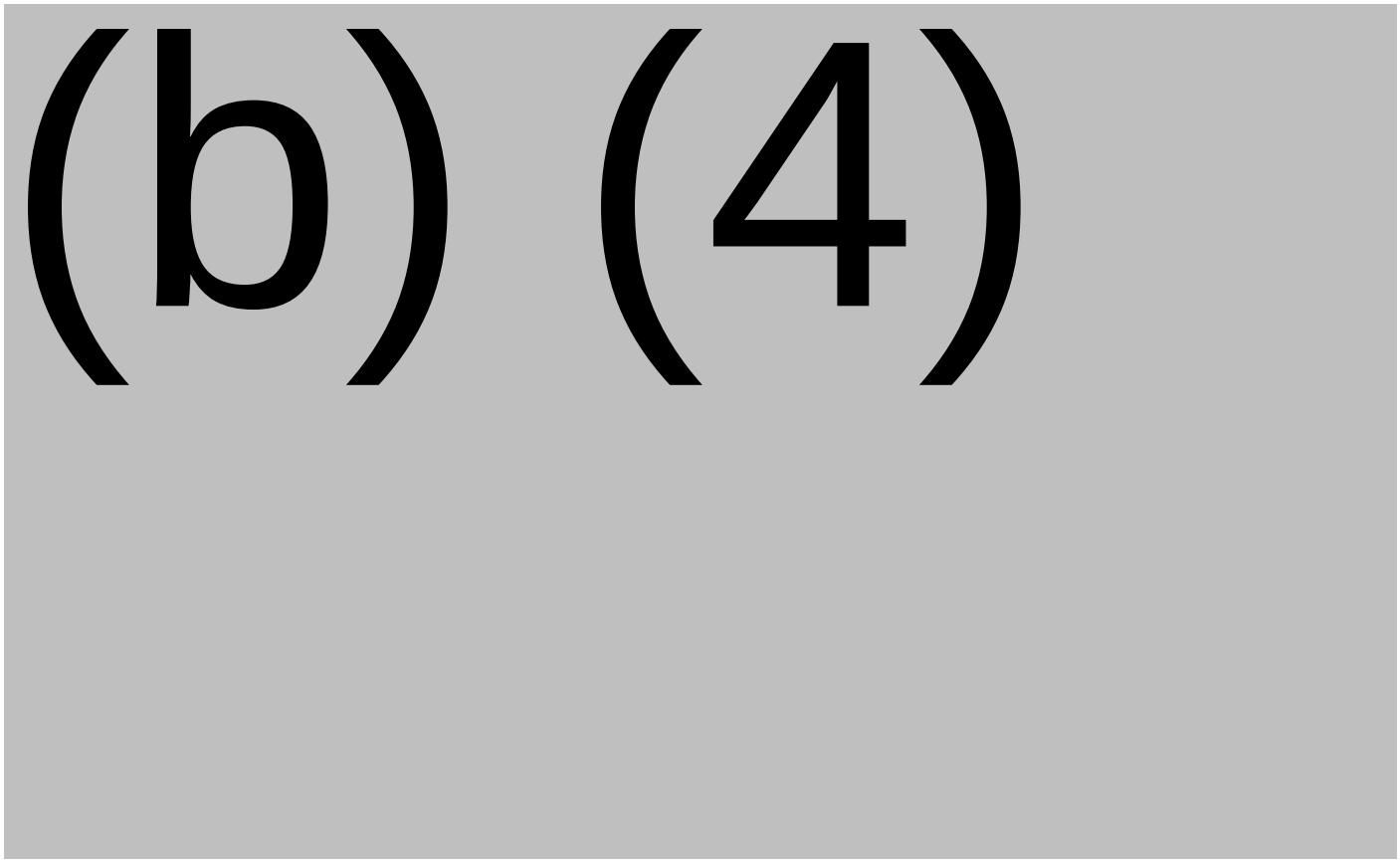
(b) (4)

None of the used test samples were screened for supposed presence or absence of antibiotics in the originating Cord Blood units.

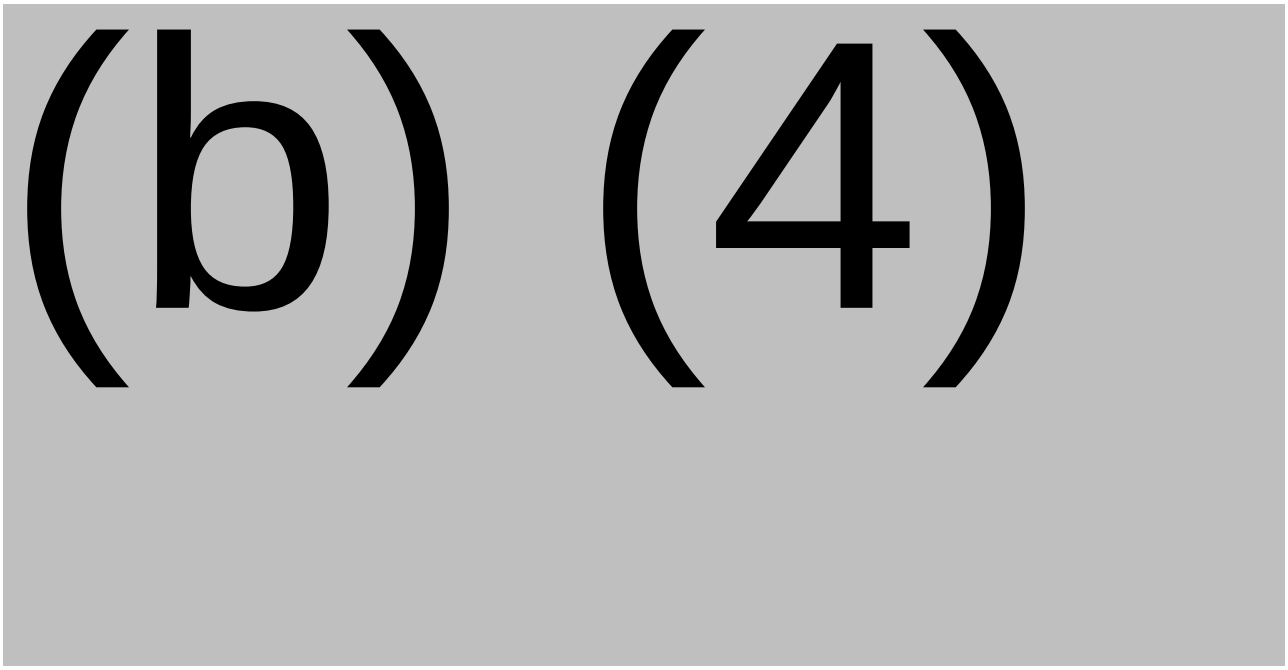
The acceptance criteria for this study were:

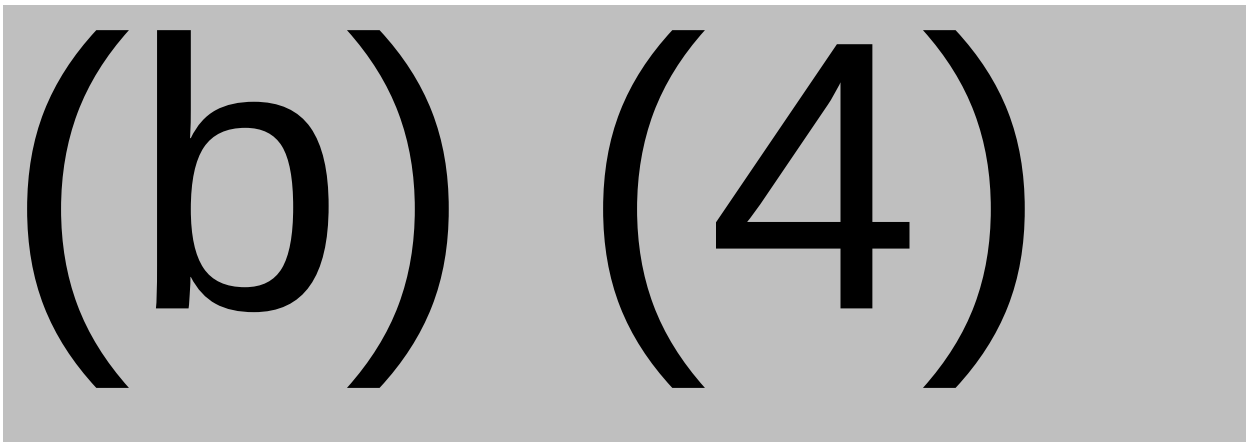
(b) (4)

Data from the method suitability study are summarized in Table 30 below.

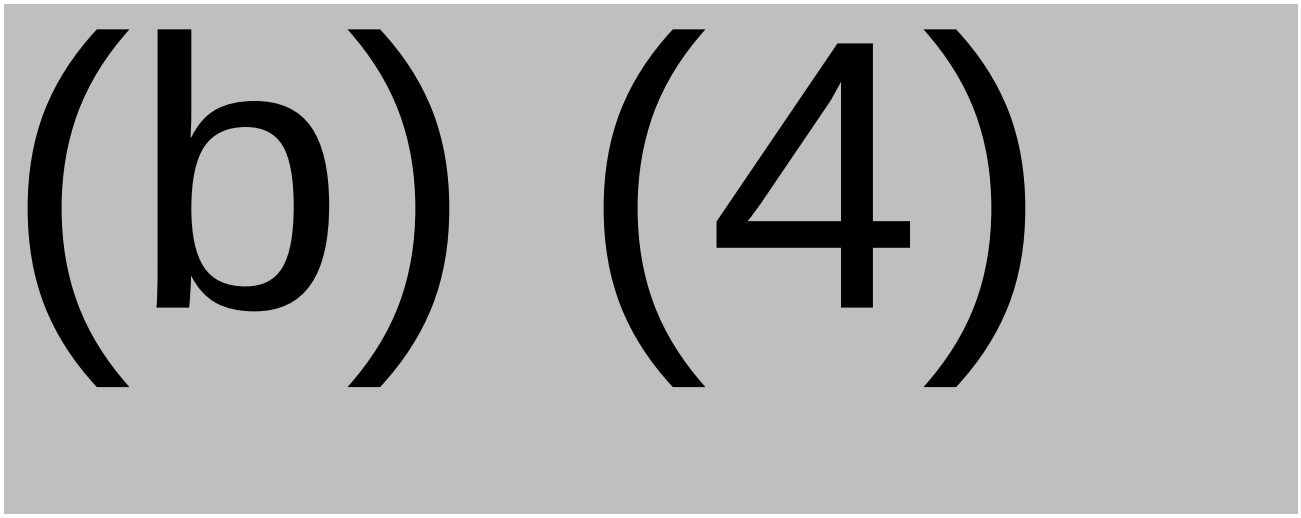


Reviewer comments:





***Reviewer Comments on Other Issues*:**



Overall Conclusion and Recommendations:

1. *The proposed Sterility Test method and Release Specifications are acceptable.*
2. *As the applicant is not excluding Cord blood units from antibiotic-treated donor mothers, we recommend that the Prescribing Information includes a warning regarding the potential of anaphylactic shock (for the sensitized recipients) from the residual antibiotics.*
3. *Due to*
    - *the inherent limitation of the sampling method used for the sterility test (especially under low bioburden conditions),*
    - *the fact that the processed HPC, Cord Blood final product is not suitable for terminal sterilization, and*
    - *the inability of the used media to neutralize residual antibiotics,*

    we recommend that the Bloodworks HPC, Cord Blood not be labeled as 'sterile' and the Prescribing Information include a warning regarding the potential to transmit infectious bacteria or fungi.

BLOODWORKS QUALITY UNIT:

The applicant states that their Quality Unit has the following responsibilities (per SOP CBP 2300 "Quality Control Unit (QCU) Responsibilities" and BCQ 0001 "Quality Program"):

- Approve or reject all components, drug product containers and closures, in-process materials, packaging, labeling, and HPC, Cord Blood units.
- Review production records to ensure no errors have occurred and that those that do occur are fully investigated.
- Approve or reject procedures/specifications affecting identity, strength, quality, and purity of HPC, Cord Blood.
- Review and approve written procedures for production and process control, including any changes to these procedures.
- Review and approve the establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, including any changes in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms.
- Review and approve all HPC, Cord Blood production and control records to determine compliance with all established, approved, written procedures before a lot is released or distributed. Any discrepancies must be thoroughly investigated.
- Establish and follow written procedures describing the handling of all written or oral complaints, including provisions for QCU review of any complaint related to "HPC, Cord Blood" failures; investigation of any complaint; evaluation of whether the complaint represents an adverse drug experience and, if so properly reporting it.
- Periodically conduct internal quality audit.

These activities are performed by the Quality Assurance and Regulatory Affairs department (QA/RA) and Cord Blood Services (CBS) Quality Control Unit (QCU) and includes the following individuals:

QA/RA Director
Quality Assurance Officer
Quality System Specialist
Medical Director
Cord Blood Services (CBS) Program Director
Collections Manager
Laboratory Manager

The applicant states their Quality Assurance and Regulatory Affairs department (QA/RA) is an independent and ultimate authority to objectively approve or reject products.

***Reviewer comment**: Inclusion of collection and lab managers in quality unit system is managed by having QA/RA as an independent authority to objectively approve and reject products. This quality unit system appears to be designed adequately to control the manufacturing process and product quality.*

RELEASE FROM QUARANTINE STATUS:

After processing, HPC, Cord Blood units are stored in a quarantine liquid nitrogen freezer until the results of all exclusion criteria have been determined. If all exclusion criteria have been determined and found to be negative, and the donor chart is reviewed and signed off, a unit will then be transferred to a 'Full Release' status. A QA Specialist will complete the Inventory Status Change Request Form and deliver to Cell Processing Lab technologists who will perform the physical transfer. If a CBU fails to meet any HPC, Cord Blood standard for transplant suitability (per SOP CBP 1060, "HPC, Cord Blood Criteria Policy") it cannot be released for transplant (use SOP CBP 5050, "Disposition Change of HPC (CB)". Unsuitable units and all of its remaining products are quarantined until a disposition is determined, e.g. discard (e.g. positive/reactive donor infectious disease test results), release for research, or hold for purposes of quality assessment (QA hold, e.g. CBU that didn't meet donor eligibility criteria due to a parent with an autoimmune disease). Units that do not pass exclusion criteria need to be transferred to a research or QA Hold storage location or discarded.

COMPUTER SYSTEMS and CBU RESGISTRY LISTING:
(Please see DMPQ review for additional details)

• Blood Bank Control System (BBCS):
The Blood Bank Control System (BBCS) software tracking system is a (b) (4) developed by (b) (4) . Bloodworks CBS Donation Coordinators use the Blood Bank Control System (BBCS) software (version 5.3.7) to register and track the CBU donor via a unique BBSC Donor ID number and keep records of the donor's infectious disease testing, screening, and donation history, per SOP CBP 3056, "Registering a Cord Blood Donor in BBCS".

• Bloodworks Cord Blood Database:
The Cord Blood Database (b) (4) based database used for data transfer, data tracking and statistical analysis. During the technical review of the batch record (per SOP CBP 8020, "Performing Technical Review"), Cell Processing Lab Technologists enter the CBU information into the Bloodworks Cord Blood Database per SOP CBP 7071, "Performing Cord Blood Database Entry for (b) (4) HPC, Cord Blood Products". The Cord Blood Database

includes information on CBU collection, receipt processing, product testing, cryopreservation and storage location data. The resultant "CBU Summary Sheet" extracts data from the BBCS and Cord Blood Database and filed in the batch record for subsequent final technical, medical, and quality review. The Cord Blood Database is used to generate an (b) (4) file which is uploaded to the (b) (4) (see below).

• (b) (4) Database System:
The National Marrow Donor Program (NMDP) web based (b) (4)) software application allows transplant facilities to search and request available CBUs for further testing and transplantation and allows users to track fulfillment of various order types (confirmatory Typing, hold, and CBU shipment requests). Bloodworks creates and uploads (b) (4) format files containing CBU information (e.g. maternal samples, confirmatory testing) for "HPC, Cord Blood" units that are suitable for transplantation and available for search, per SOP CBP (b) (4) Upload and Entry". The final NMDP Data Transfer Report (Crystal Report) is printed, reviewed for accuracy, completeness, and filed in the donor batch record chart prior to submitting the HPC, Cord Blood unit for search in (b) (4).

• (b) (4) :
The (b) (4) instruments and software are (b) (4) cleared (table below):

(b) (4)

SELECTION REQUEST MANAGEMENT:

Bloodworks' HPC, Cord Blood units are distributed through the National Cord Blood Coordinating Center operated by the National Marrow Donor Program (NMDP). Transplant centers search NMDP's database containing specific, detailed reports for all of Bloodworks' HPC, Cord Blood units available for shipment via (b) (4), NMDP's electronic inventory, search, and shipment control system. While all CBUs are HLA typed at the time of processing and release into inventory, a second, confirmatory HLA typing (preferably from an attached segment) is required for shipping a HPC, Cord Blood unit for transplant. The transplant center requests confirmatory HLA typing on a CBU prior to selecting the unit for transplant. NMDP staff place a confirmatory typing (CT) request in (b) (4) for Bloodworks to ship a sample to the NMDP contract lab (b) (4) . A segment or a viable cell aliquot is removed and documented per Form 25-9-073, "HPC, Cord Blood Sample Request Form". The sample is sent in an (b) (4) . NMDP (b) (4)

(b) (4) uploads the HLA results in (b) (4) and Bloodworks CBS Medical Director reviews them during the CBU order process (see below).

BATCH ANALYSIS AND RELEASE TO TRANSPLANT CENTERS:

The transplant center's CBU order/shipment request is initiated and handled by an NMDP Case Manager (CM) via (b) (4) for Bloodworks CBS to reserve the CBU. When an HPC, Cord Blood unit is ordered by a transplant center, and while awaiting confirmatory HLA typing results, the CBU's batch record undergoes final review and sign-off. Both the medical director and QA officer review requirements for release and sign the accompanying forms for shipment per SOP CBP 7010, "Processing an HPC, Cord Blood Order". Prior to the release of the unit, CBS staff completes and Medical Director reviews Form 25-9-174, "HPC, Cord Blood Release Specifications for Distribution", comparing the form to the batch record. The Medical Director also signs off on the HLA Confirmatory Typing results after verifying accuracy when compared to original HLA test results in the batch record. The Medical Director determines final eligibility of the CBU reviewing the batch record using Form 25-9-179, "HPC, Cord Blood Final Eligibility Determination". After the Medical Director's review is complete, the QA Officer reviews the medical signoff sheets, shipping documentation details, and conducts the final pre-shipment review. Completed documents and the batch record are reviewed and released by a member of the Quality Systems Unit (e.g. Bloodworks Quality Systems Specialist). Form 25-9-174, "HPC, Cord Blood Release Specifications for Distribution" is signed by the Bloodworks Quality Systems Specialist to document the final release of the CBU.

CBU ORDER SHIPMENT:

The HPC, Cord Blood unit and samples are retrieved from the storage freezer with a second CBS staff member for identification verification. The unit and samples are removed from the storage freezer and placed into the LN2 dry shipper. After documenting that the CBU has been retrieved, the CBU and samples are secured by sealing the temperature monitor lid with a zip tag. Accompanying documentation and (b) (4) Ships Log temperature monitor device (b) (4)) are located inside the outer shell container lid of the dry shipper. The (b) (4) Ships Log records temperatures at (b) (4) intervals and is set to trigger a recorded alarm at temperatures warmer than -150°C and its settings are verified prior to use per SOPs CBP 7020 and CBP 9085. A second staff member verifies delivery address and documents completion of these steps on Form 25-9-090, "HPC, Cord Blood Shipping Checklist".

Cryopreserved HPC, Cord Blood units are transported to transplant centers using charged liquid nitrogen dry shippers (b) (4)). Prior to being placed into service, charged liquid nitrogen dry shippers are qualified to maintain internal temperatures of ≤ -150°C for a minimum of (b) (4) and receive (b) (4) preventive maintenance per SOP CBP 9250. All dry-shippers are requested to be returned to Bloodworks CBS. Upon Bloodworks' receipt of the LN2 dry shipper, the data from the Ships Log temperature monitor are downloaded and printed for review as per SOP CBP 9085. Additional receipt documentation (re: Form 25-9-053, "Shipping Information") and NMDP's Receipt of Cord Blood Unit are sent by the transplant

center electronically and are reviewed and filed in Bloodworks' batch record. Any excursions of temperature during transport of HPC, Cord Blood are investigated with the receiving transplant center. Bloodworks CBS typically ships (b) (4) CBUs per (b) (4), with a range from (b) (4), resulting in just over (b) (4) shipments to transplant centers in one year.

ENVIRONMENTAL ASSESSMENT:

The applicant requests categorical exclusion for their HPC, Cord Blood product citing 21 CFR 25.31(c) and state that the HPC, Cord Blood substance occurs naturally in the environment. The applicant states this action does not alter significantly the concentration or distribution of the substances, its metabolites or degradation products in the environment. Categorical exclusion per 21 CFR 25.31 (c) will be addressed by DMPQ.

SHIPPING:

Shipping from collection site to the processing facility:

Bloodworks Cord Blood Program will be receiving the CBUs from 17 collection sites/partners. These collection sites are located in Washington (9 sites), Oregon (1 site), Hawaii (6 sites) and a collection partner in Hawaii (1 site). Depending on the distance from collection site to the Cord Blood Services processing laboratory, either a (b) (4) Insulated Styrofoam Shipper (long distance shipper) or a (b) (4) Plastic Transportation Container (local shipper) is used for packaging and shipping of collected CBUs as per SOP CBP 4070. CBUs collected in Hawaii, Oregon, and Central Washington (Yakima) are packaged in (b) (4) Insulated Styrofoam Shipper. The rest of the collecting facilities utilize (b) (4) Plastic Transportation Container. Labeled CBU and maternal samples are placed in zip top bag wrapped in a gel wrap along with the completed paper work (Cord Blood Donor Short Screening and Update Form (25-9-106), Mother's Consent to Donate Cord Blood (25-9-001), Delivery Information Form (25-9-021), and Maternal Samples form (25-9-136). The temperature in transit is maintained between (b) (4). CBUs that fall outside this range between collection and receipt in the processing facility are discarded (SOP CBP 4060). The temperature was initially maintained using (b) (4), which was discontinued in January 2014. The temperature is now maintained using (b) (4).

Local transport was handled by Bloodworks transportation department couriers. Long distance transport was handled by (b) (4).

(b) (4)

Reviewer comment: *It was unclear from the submitted materials how the actual elapsed shipping and handling times along with the ambient temperature conditions encountered for cord blood shipments compare to applicant's shipping plan and the validated conditions of the containers used for shipping cord blood. In response to above query, the applicant provided the timings for actual shipping in amendment 1 (29 April, 2015). Note: Based on the information provided by the applicant in amendment 1, it was noted that some of the shipments took longer than* (b) (4) *the shippers were validated for. The discrepancy in the shipper validation was brought to the attention of the applicant during Pre-licensing inspection (July 13-17, 2015). The applicant responded by mentioning that irrespective of duration of the shipper validation, all shippers will be accompanied by the* (b) (4) *temperature monitoring device* (b) (4) *). History of temperature logged will be monitored from the collection site to the Cord Blood Services processing laboratory. CBUs that fall outside the range* (b) (4) *between collection and receipt in the processing facility will be discarded. The applicant's response is adequate.*

Shipping from Bloodworks to Transplant Center:

Bloodworks ships the CBUs to the transplant centers worldwide. The CBUs are shipped using the (b) (4)) in "dry" Liquid Nitrogen (LN_2) shipping (b) (4) that maintains ≤ -150°C temperatures (SOP CBP 7020). The (b) (4) is designed for the safe transportation of biological products and samples at cryogenic temperatures. It employs a (b) (4) that retains liquid nitrogen. The samples to be transported are held in the (b) (4) of the liquid nitrogen during shipment. The outer walls of the shipper contain a vacuum seal that allows minimal temperature change due to external environment. The (b) (4) fits into a (b) (4) , designed to protect the shipper in transit. The shipper can hold temperature at ≤ -150°C for more than (b) (4).

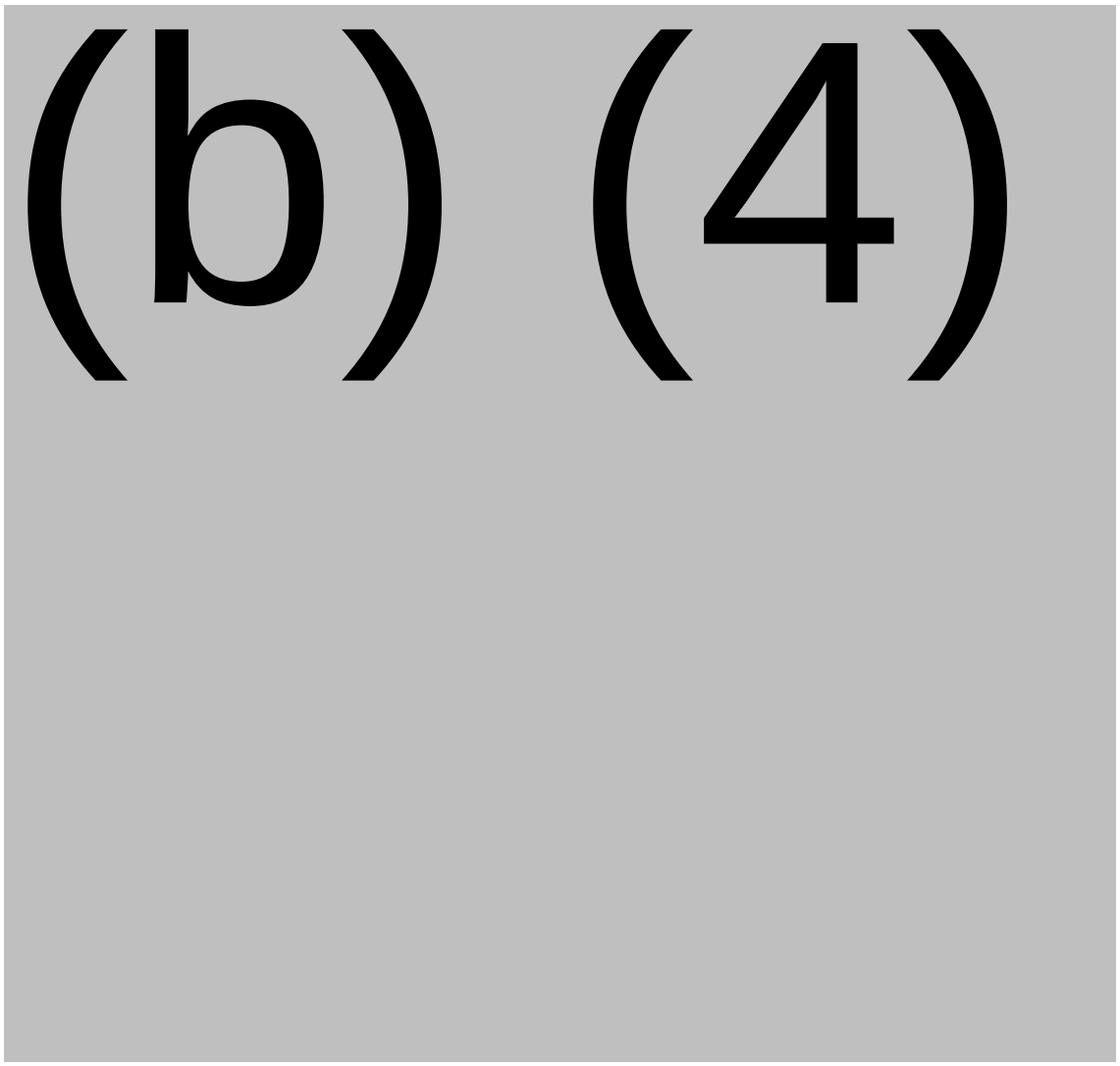
Once a cord blood unit is selected by a transplant center, National Marrow Donor Program (NMDP) assigns a case manager and the details of the ordering and shipment (unit ID and sample requests, shipment date, and transportation courier) of the CBU. Cord Blood unit is then shipped to the transplant center and the sharing of data necessary for the transaction are managed by the case manager and the (b) (4)) database.

Upon delivery of Cord Blood unit at a Transplant center, the Transplant center staff completes the enclosed NMPD Form 600 and transmits copy to NMDP. This form details the condition of the shipment upon arrival at the Transplant center. NMDP displays this form in (b) (4) for viewing by the (shipping) cord blood bank. Communication from a case manager occurs if a shipping problem occurs such as late/delayed delivery or shipping loss/damage.

Upon receipt of the returned shipper, Cord Blood Services recovers enclosed shipping forms and evaluates the physical condition of the shipment, condition of temperature monitor, and the date and time of arrival at the Transplant center. Data from the temperature monitor is retrieved and evaluated against details listed in the enclosed shipping forms and the acceptability of the shipment is determined. If acceptable, the batch record is amended to reflect the acceptable shipment; if not acceptable, Cord Blood Services Medical Director, NMDP, and the transplant center are notified and an investigation into the discrepancy occurs.

(b) (4) :

(b) (4)



The applicant has submitted the data on the actual shipments demonstrating that the shippers were able to maintain specified temperature of ≤ -150^{o}C for the duration of the shipment. The typical time for the above shipments was (b) (4)

Reviewer comment: *The dry shipper validation data was found to be adequate to support the receipt of the CBUs with the intact container closure and at the recommended temperature (≤ -150^{o}C).*

LOT RELEASE TESTING:

Safety:

Hemoglobin Testing:

Hemoglobin is tested for homozygous hemoglobinopathies. Cord Blood Units are not acceptable for distribution if they contain evidence of homozygous variants hemoglobin or multiple heterozygous hemoglobin abnormal variants. In order to make this determination hemoglobin in the red cells of each cord blood unit undergoes testing. Results are reviewed by the medical director to assure that only normal or single heterozygous hemoglobin combinations are released into inventory.

Hemoglobin testing is performed by Washington State Department of Health (DOH) Lab for residents of the state of Washington (SOP CBP 6150). Residents of Oregon and Hawaii are not tested in laboratories amenable to data-sharing agreements. So the samples from cord blood units from those states are sent to a contract laboratory at the Children's Hospital and Research Center at Oakland (SOP CBP 6135).

Washington State Department of Health (DOH) Lab (CLIA: 50D0661453, 50DO869979) and Children's Hospital and Research Center at Oakland (CLIA: 05D0698497).

Validation of Hemoglobin Testing:

Both the Children's Hospital and Research Center at Oakland, CA and the Washington State DOH Lab were qualified via the Bloodworks supplier qualification process, as described in SOP BCQ 0502. Both the labs are qualified on the basis of existence of a quality program, Observance of GMP, test result problem/recall notification, customer complaint handling system and CLIA certification.

Reviewer comment: *Hemoglobin testing was found to be satisfactory as both the Children's Hospital and Research Center at Oakland, CA and the Washington State DOH Lab are CLIA certified and are qualified by Bloodworks.*

Purity and Potency:

Total Nucleated Count: (b) (4) .

Total Nucleated Count is done on the (b) (4) , which is located at Bloodworks Testing Lab (b) (4)). The system is used to generate a report of CBC, WBC with Diff and nRBC to determine total nucleated cell count (TNC) of incoming collected cord blood, cord blood post-processing, and thawed HPC, Cord Blood products.

The (b) (4) system consists of a (b) (4) , information processing unit, a monitor, printer, and uninterrupted power supply unit. All Cord Blood samples are analyzed in (b) (4) mode, which allows for (b) (4) . In this mode, the sample is (b) (4) Results are generated via Sample Explorer software and printed. Originals are kept with the system documentation as the

document of record, and copies are distributed to Cord Blood Services for integration into batch records.
The table below gives the overview of the TNC timings:

TABLE 33. Sample Preparation for TNC Count

Sample	Sample preparation instructions	Component type	Timeline	Purpose of Testing
Whole cord blood (WB or PRE)	SOP CBP 5130	Fresh, cord blood in CPD	Before processing	Evaluate cell substance TNC
Final product (FP or DFP)	SOP CBP 5135	HPC, Cord Blood product, diluted with plasma	Post-processing	Evaluate final TNC and recovery
Thawed final product (TFP)	SOP CBP 7031	HPC, Cord Blood, reconstituted with LMD/HSA solution	Post-thaw	Evaluate post-thaw TNC and recovery

Results are reviewed by the operator and report is supplied to the Cord Blood laboratory. Nucleated red blood cells (nRBC) are included in the complete blood count (CBC) under "NRBC+W" (uncorrected WBC). If the unit is selected for further processing and either the nRBC is (b) (4) or results for any parameters were not reported by the analyzer, a (b) (4) slide is prepared for the sample. This slide is evaluated by the Medical Director for acceptability.
CBC results are received by the Cord Blood laboratory and used with the following formula to calculate TNC:

TNC= Uncorrected WBC X Volume remaining in container after sampling.

In event of the unavailability of the (b) (4) for an extended period of (b) (4)), the TNC will be provided by qualified vendor (b) (4) The above mention vendor is CLIA certified (b) (4)

(b) (4)

Reviewer comment: (b) (4) *TNC qualification and validation was found to be adequate. TNC is performed on FDA cleared instrument (*(b) (4) *). The instrument is daily evaluated for the proper functioning along with* (b) (4) *maintenance performed by the technologist recommended by* (b) (4) *operator's manual. All the calibration documents were evaluated during the site inspection in July 2015. As a backup plan the applicant has a CLIA certified vendor, who will perform the TNC. Training records on the technicians were examined during the inspection and were found to be complete and up-to-date.*

Cell Viability: (b) (4)):

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer comment: *During the inspection it was observed that SOP CBP 6010 was not found current, the* (b) (4) *counting using* (b) (4) *was stated as to be used as the backup method for the* (b) (4) *which is no longer in use. It was also found during the inspection that there was confusion in the expiry date labelling of the working stock of* (b) (4) *was dated as August 2015, whereas SOP CBP 6010 dictates the date to be within* (b) (4) *which deviates from the SOP CBP 6010. Of note, these issues were included as inspectional observations on Form FDA 483 issued during the July 2015 inspection. The applicant has responded to above citations and has taken appropriate corrective measures.*

Colony Forming cells (CFU) Assay:

Hematopoietic stem cells (HSCs) present in umbilical cord blood undergo differentiation including multi-potential and lineage-specific progenitors. When cultured in a suitable semi-solid matrix, individual progenitors called colony-forming cells (CFUs) proliferate and differentiate to form discrete cell clusters or colonies containing recognizable progeny. This assay can be used to enumerate erythroid progenitors (CFU-E and BFU-E), granulocyte/macrophage progenitors (CFU-GM, CFU-M, CFU-G) and multi-potential granulocyte, erythroid, macrophage and megakaryocyte progenitors (CFU-GEMM). Under optimal plating and culture conditions, each colony is derived from a single progenitor and can be classified and enumerated based on the morphological recognition of one or more types of hematopoietic lineage cells within the colony. The enumeration of these colonies can demonstrate the qualitative potential of engraftment of a HPC, Cord Blood unit.

Method: The CFU assay is performed in Cord Blood Testing Laboratory of the Bloodworks using the (b) (4)

(b) (4)

Results: The results of the colony forming unit assay must demonstrate growth per SOP CBP 1060, "Colony Forming Assays".

(b) (4)

Reviewer comment: *CFU assay was found to be sufficiently validated. The results from* (b) (*technologists were compared and the data was found to be within +/- 2 SD. The total colonies enumerated on days* (b) (4) *fell within mean deviation of* (b) (4)*, which is acceptable. There are multiple steps enforced where the CFU data is reviewed, before the product is released to the registry. In addition only the CBUs that demonstrate the growth are approved for banking as licensed units.*

Identity:

Human Leukocyte Antigen (HLA) typing:
Initial HLA typing is done at Bloodworks. The Bloodworks Cord Blood Services Cell Processing Lab sends filter paper with a red cell sedimentation sample and an assigned National Marrow Donors Program NMDP ID number to the NMDP Repository. The NMDP cord blood unit's Identification number (CBU Registry ID) is assigned to each processed CBU at the time of selecting samples for HLA typing per SOP CBP 6140.

HLA Typing Confirmatory:
Confirmatory HLA typing is done by (b) (4), a contract lab of the National Marrow Donor Program. Replicate samples of HPC, Cord Blood are used for confirmatory HLA typing. The preferred sample for HLA typing is the attached segments from CBU. However, if an attached segment is not available, a diluted replicate aliquot created during the manufacturing of the HPC, Cord Blood unit is used. Testing samples are prepared per SOPs CBP 5135 and CBP 5140.

Methods for identifying and confirming HLA type are listed below:

(b) (4)

(b) (4)

(b) (4)

Reviewer comment: *HLA testing is adequate as all the reagents and kits used are FDA cleared and the HLA typing labs are CLIA certified along with accreditation from American Society of Histocompatibility and Immunogenetics. Also the SOPs are in place to ensure that the test results are correctly linked to the individual donors.*

Blood Group and Rh type Testing:

ABO/RH blood group is determined for the Cord Blood unit after automated processing is complete. A portion of the separated red blood cell sediment is sent to the Compatibility Laboratory, an internal lab in Bloodworks. The tests performed are FDA licensed tests, performed per Bloodworks SOP and manufacturer instructions. The CLIA number for this laboratory is (b) (4) In addition to CLIA certification, the lab also has Medical Test Site License, FDA Establishment License, and AABB Accreditation Certificate.

TABLE 35. ABO/RH licensed tests

Analyte	(b) (4)	Summary of Intended Use
ABO Group - RBC		Blood grouping monoclonal antibody antisera
ABO Group - RBC		Blood grouping monoclonal antibody, antisera
Rho factor - RBC		Monoclonal antibody serum

Reviewer comment: *The blood group testing was found to be adequate as all test systems and reagents are under CLIA high complexity testing designations.*

Viable CD34+ Flow Cytometry

Flow Cytometry/Viable CD34+ cells Validation (BLA Section 3.2.S.4.3.3)

CD34+ cell enumeration is used in the evaluation of hematopoietic progenitor cells found in HPC, Cord Blood. The quantity of $CD34^+$ cells is important in determining the suitability of a cord blood product for transplantation.

Sample: HPC, Cord Blood final product.

Rationale for CD34+ and(b) (4) Cell Enumeration and Viability as part of potency

The (b) (4) CD34/(b) (4) enumeration assay provides a measure of final product potency by quantifying the viable $CD34^+$ cells in hematopoietic progenitor cells derived from HPC, Cord Blood. The (b) (4) antigen is present on all human leucocytes and is weakly expressed on hematopoietic progenitor cells. The number of (b) (4) cells is closely related to the (b) (4). Viability measurement of the (b) (4) cells in a hematopoietic progenitor cell product can be used in lieu of (b) (4) as part of the potency for this HPC, Cord Blood product.

Expected Results

The minimum acceptable viable nucleated cells (b) (4) cell viability for an HPC, Cord Blood product is ≥ 85%. The minimum acceptable viable $CD34^+$ cell content of an HPC, Cord Blood product is ≥ 1.25×10^6.

Description of Protocol

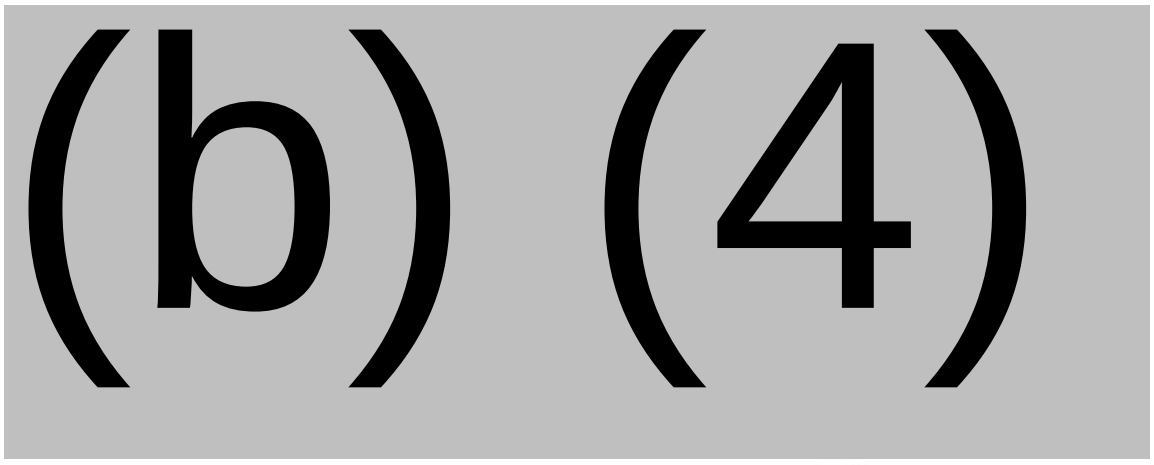
(b) (4)

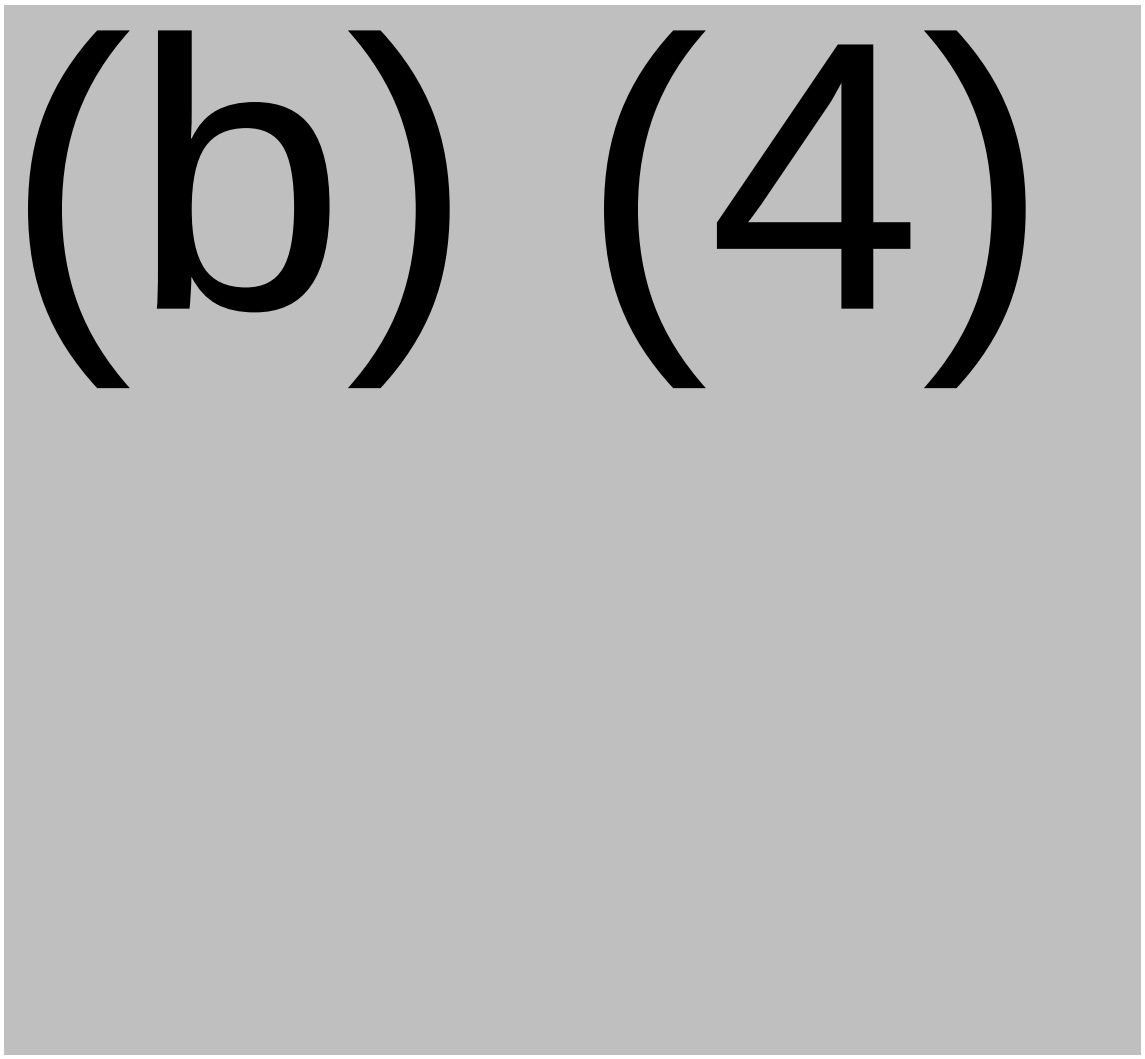
(b) (4)

(b) (4)

Results

Data are analyzed using commercial (b) (4), for acquisition and analysis on (b) (4) (SOPs CBP 9400 and CBP 6170) and (b) (4) package for acquisition and analysis on (b) (4) (SOP CBP 9410). Figure 6 shows the flow cytometry gating template and representative data analysis.





Flow cytometry validation summary

(b) (4)

(b) (4)

Instrument Controls

(b) (4)

.

Equipment

(b) (4)

Reviewer comment: *The applicant states that "Cord Blood Services will utilize an additional* (b) (4) *system as backup, instead of a* (b) (4) *system. This backup instrument is located in Donor Testing laboratory. The IQ/OQ/PQ for this system will mirror the current* (b) (4) *validation and validation data will be submitted once they become available." This was in response to an FDA request to submit the proposed validation plan for the backup instrument. In 125585/0/1, the applicant agreed that accuracy, precision, and linearity tests will be used to validate new instruments. Also, the firm provided additional data regarding requested employee training records. This is acceptable.*

Development of Validation Approach for CD34+ and (b) (4) cell count and Viability

The validation was developed over the time period 04-2012 to 08-2013 with the aid of (b) (4) representatives and various Cord Blood Services personnel. The protocol evaluated: general operation of the equipment, equipment performance during operation at production level conditions, and assay performance; in terms of linearity, accuracy, precision and robustness.

Equipment validation requirements include:

(b) (4)

Assay Validation

- Linearity:

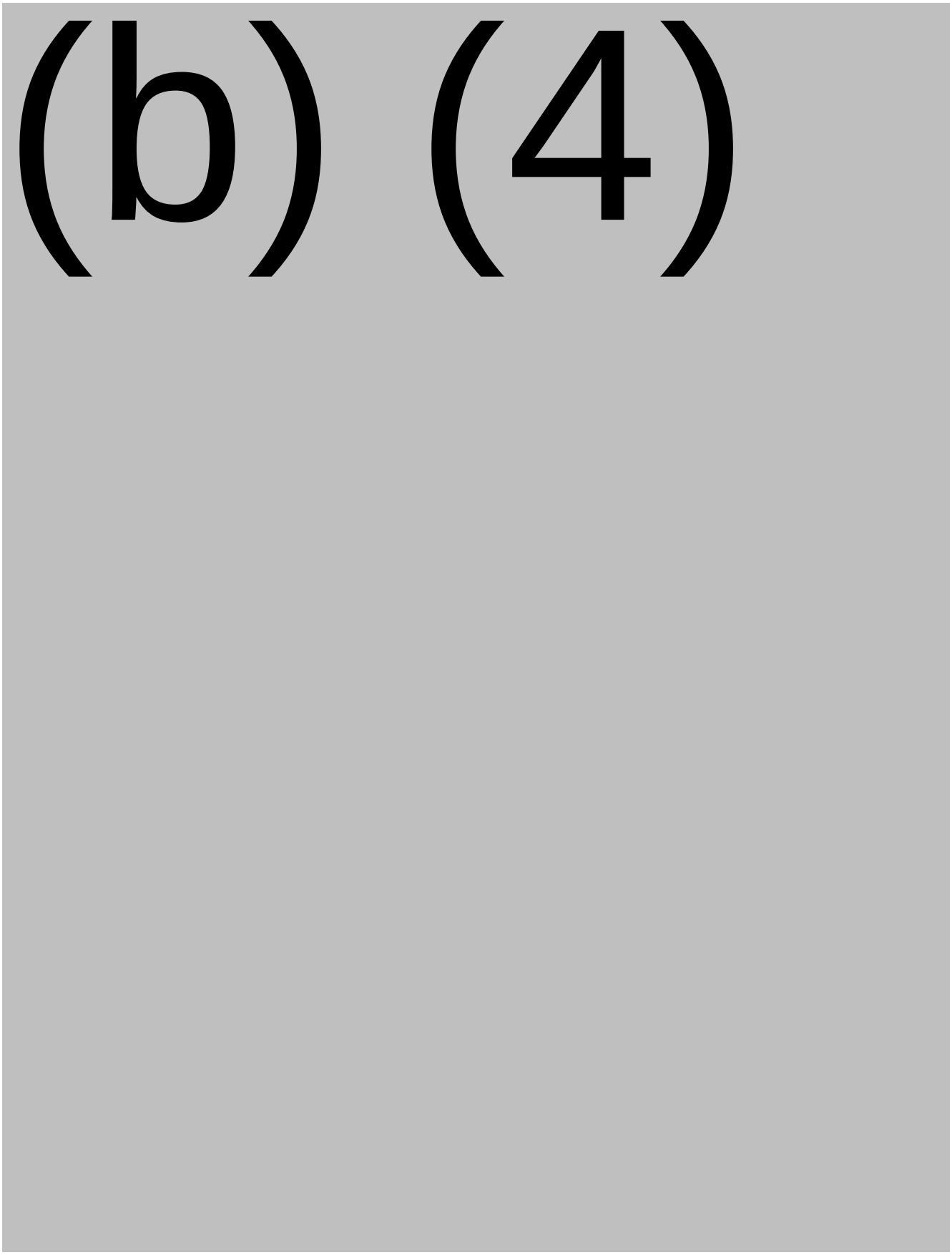
CD34 and (b) (4): a control sample derived from post-processing HPC, Cord Blood with a known CD34(b) (4) value. The volume of final product for dilution used range from (b) (4)

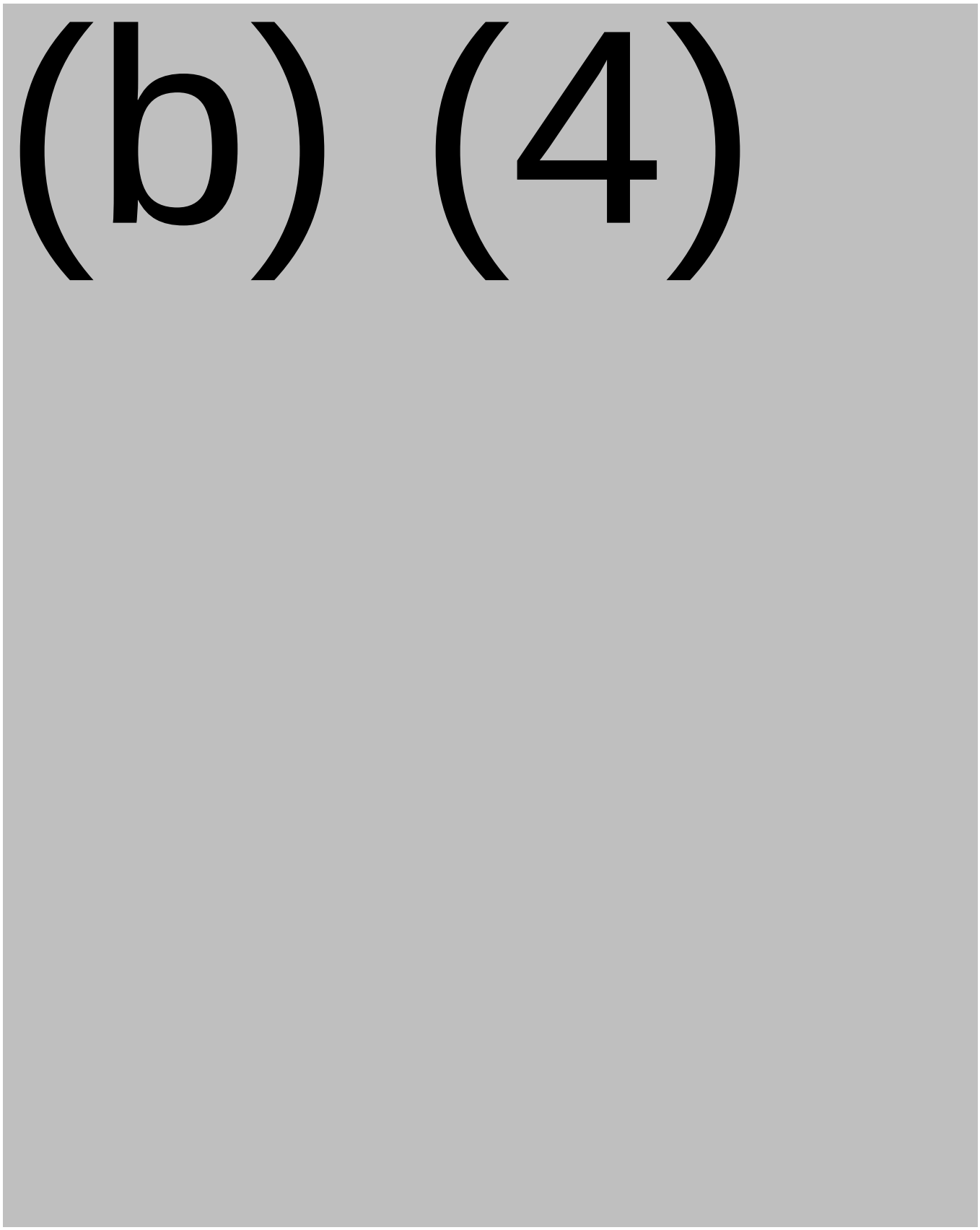
(b) (4)

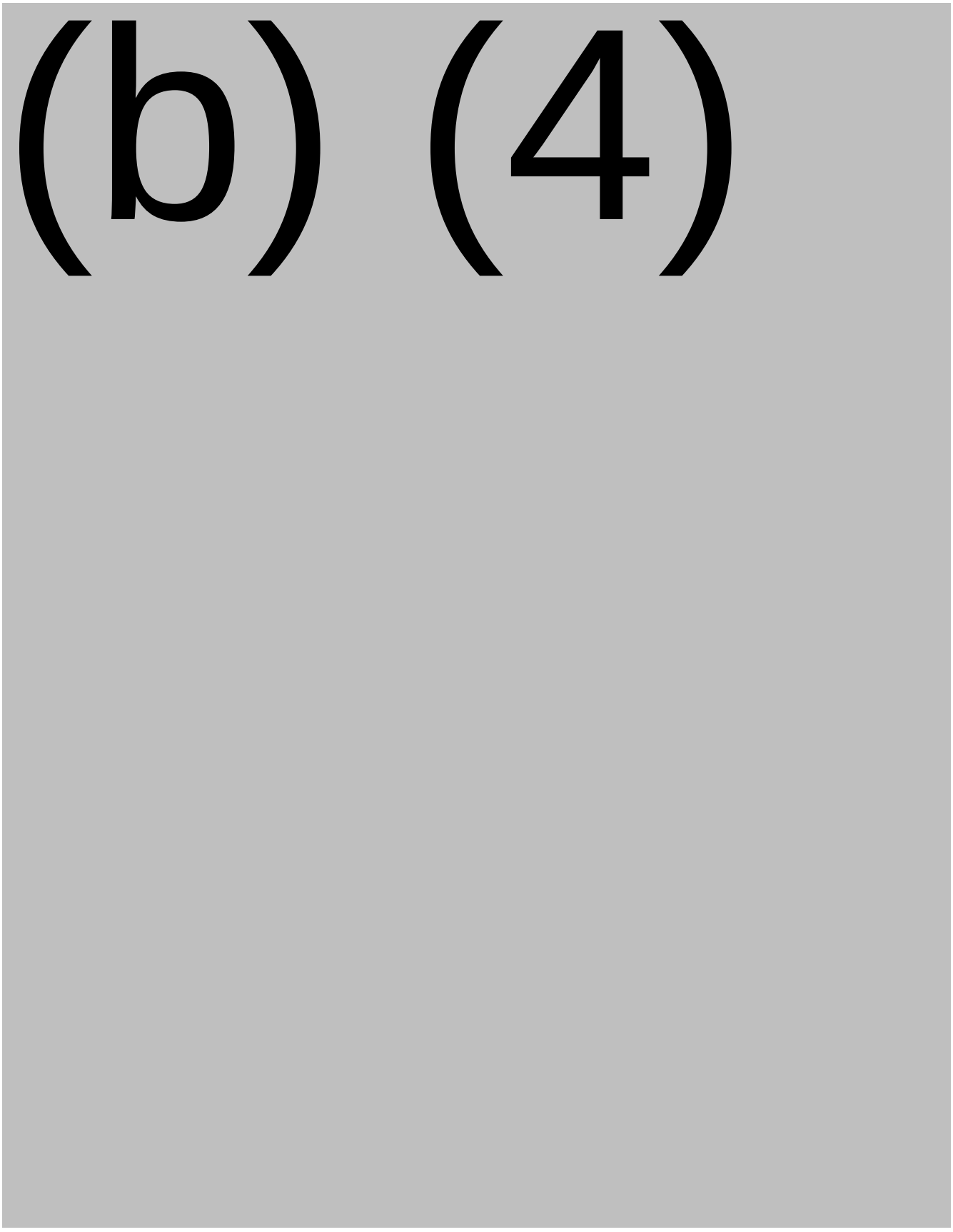
(b) (4)

TABLE 36. Viable CD34+ Flow Cytometry Validation Plan and Results

(b) (4)

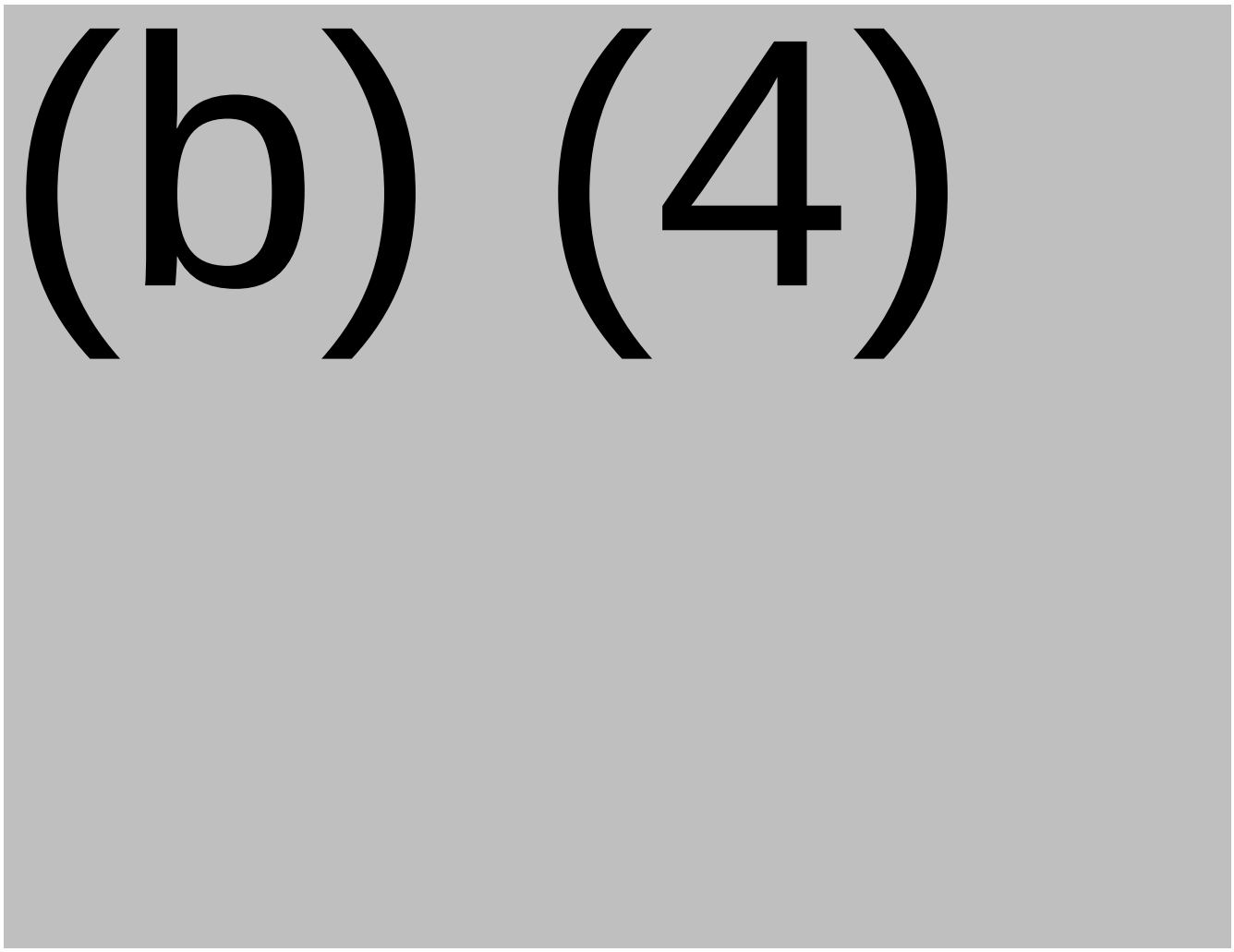

(b) (4)


(b) (4)


(b) (4)

(b) (4)

TABLE 37. CD34+ Flow Cytometry Method (b) (4)



Reviewer comment: *The applicant has adequately demonstrated the Accuracy, Precision. Linearity and Robustness of the flow cytometry assay as part of the potency lot release testing for their HPC, Cord Blood product.*

Post-Stain Sample Holding Time

(b) (4)

(b) (4)

(b) (4)

Reviewer comment: *While a significant shift in viable CD34+ values was observed at* (b) (4) *hours post-stain, test results indicate that viable CD34+ cell counts are maintained in the stained samples that were held for* (b) (4) *after staining and before addition of* (b) (4) *prior to sample acquisition. SOPs CBP 6210 and CBP 6250 has been revised to include the following: "Following the room temperature* (b) (4) *samples may be held, refrigerated, for up to* (b) (*prior to analysis"*

Flow Cytometry Reagent Lot Qualification

SOP CBP 6251, "Flow Cytometry Reagent Lot Qualification" provides instructions for qualification of new flow cytometry reagent lots. Lot is acceptable if qualifying lot CD34 results are within (b) (4) of CD34 results given by current lot and the control tube is acceptable per SOP CBP 6250. Reagents that do not meet the required acceptance criteria are not used for product characterization.

Additional Information on Flow Cytometry, Instrument Quality Controls

Employee Training

Cord Blood Service maintains training records for all technical and supervisory staff. Training records for additional employees performing the validation work have been submitted based on FDA request.

Instrument Quality Control and Maintenance

Cord Blood Service performs instrument quality control according to the current version of SOPs CBP 6250, "Calibration, QC, and CD34 Acquisition and Analysis on the (b) (4)", SOP CBP 6210, "Sample Preparation for CD34 Flow Cytometric Analysis: (b) (4) , Controls and Human Hematopoietic Progenitor Cell Samples", SOP CBP 6170, "CD34 Data Acquisition and Analysis by Flow Cytometry: Instrument calibration and HPC Assessment."

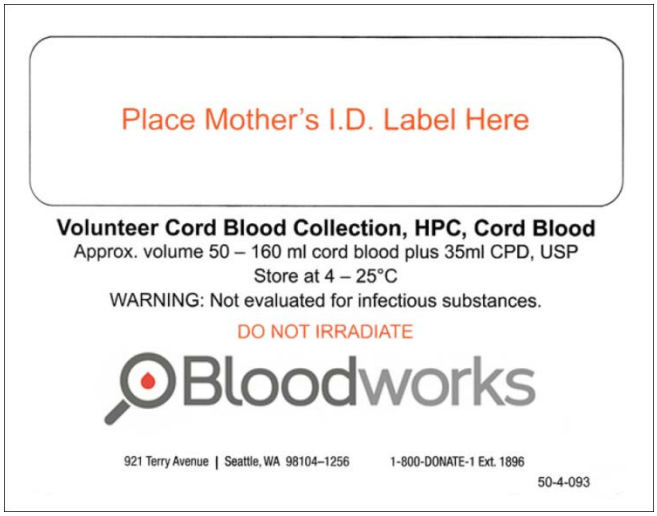
Overall Review Assessment for Flow Cytometry:

The applicant has adequately validated the flow cytometry assay used to demonstrate potency. In addition, the SOPs, instrument qualification, reagent qualification, and quality controls of the assay are adequate to ensure consistent performance of this assay as a part of manufacturing control. The flow cytometry laboratory has adequate procedures for instrument quality control, instrument validation, installation of new flow cytometers, and training of staff.

LABELING and TRACKING

At the collection sites, cord blood units, Delivery Information Form, and Maternal Samples form are labeled with hospital generated maternal identification labels which include the birth mother's name, date of birth and medical record number.

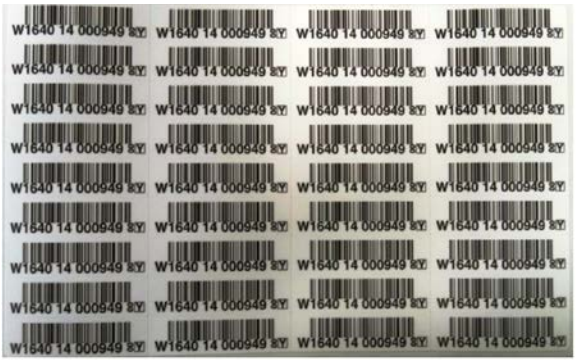
FIGURE 7. Collection Bag Label



Upon receipt, the processing facility assigns a unique donation identification number to each unit. Bloodworks uses the ISBT 128 data structure for the Donation Identification Number (DIN). The sequenced ISBT 128 barcode label sets are purchased from an outside vendor, (b) (4) The ISBT 128 number includes the facility identification number (FIN), 2-digit year and 6-digit serialized unique identifier. To protect donor's confidentiality and for tracking purposes, the unit DIN is used on all product containers, samples, forms and documents pertaining to collection, processing and distribution. Unused DIN labels are securely attached to the unit batch record. The donor's demographic information is also entered into the Blood Bank Computer System (BBCS) to obtain a BBCS donor ID #. The donor information in the BBCS is electronically transferred to the Cord Blood Database and the BBCS ID# and the DIN are automatically linked. (BLA module 1: 1.6.4, module 3: 3.2.P.5.7.4, SOP CBP 4050).

Reviewer comment: *The applicant submitted the revised collection label that includes the new facility name (email submission 12/18/15).*

FIGURE 8. Example of Local DIN Barcode Labels



ISBT 128 DINs with prefix “W1640” are assigned to the cord blood units and DINs with prefix “W1416” are assigned to the maternal specimens for infectious disease testing.

Reviewer comment: *In the original submission, discrepant information was provided regarding the prefix for the DINs assigned to the maternal specimens (On batch record examples: prefix W1416, in BLA module 3: 3.2.P.5: prefix W1614). In Amendment 2, the applicant confirmed that DINs with pre-fix W1416 are assigned to the maternal specimens.*

An individual NMDP unit and maternal ID are also assigned when a unit is selected for transplantation through NMDP. To maintain linkage, the BBCS donor ID#, the unit DIN and the maternal specimen DIN assigned by the cord blood bank, and the NMDP ID#s are all recorded on the Delivery Information Form (25-9-021).

The following are the labels that are applied after completion of processing and at the time of distribution (BLA module 1: 1.14):

FIGURE 9. Partial label affixed to the container at completion of processing

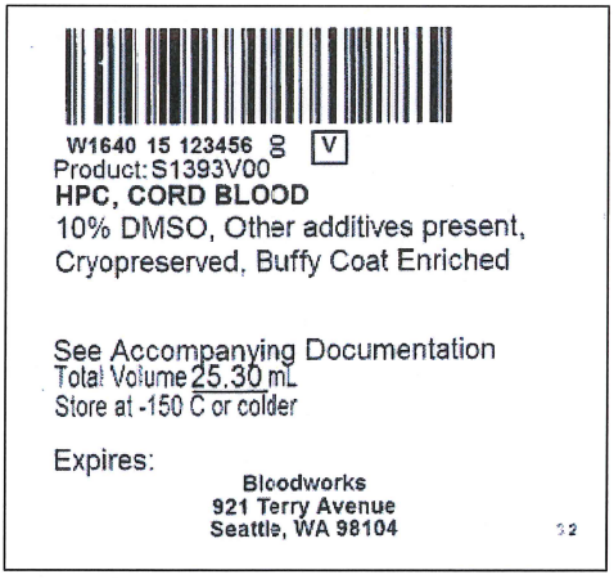
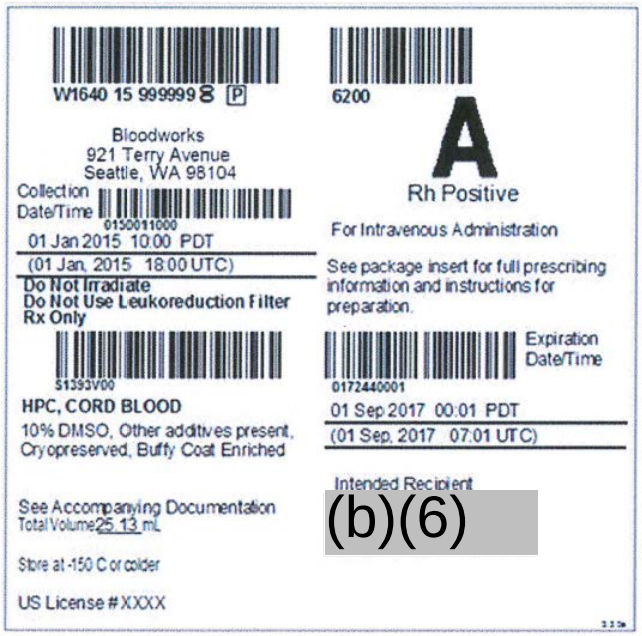


FIGURE 10. Final package label at time of distribution



At the time of distribution, the cryopreserved bag is placed in the chilled cassette that is pre-labeled with the above final label that includes the expiration date of the product.

Reviewer comment: *The applicant is planning to use the ISBT 128 labeling standards in lieu of an NDC number and has requested an exemption from the barcode label requirements. The applicant was informed that the submitted package label example did not represent a fully implemented ISBT 128 labeling system. In Amendment 2, the applicant submitted the revised final package label. Additionally, because of the facility name change, the applicant had to revise the partial and final package labels. The revised labels (figure 9 & 10) were submitted in Amendment 4. The submitted revised labels are acceptable.*