



MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

To: Administrative File STN 125657

From: Joyce Rockwell, Consumer Safety Officer, Division of Manufacturing and Product Quality (DMPQ), Manufacturing Review Branch 1(MRB1)

Through: Carolyn Renshaw, Chief, Division of Manufacturing and Product Quality (DMPQ), Manufacturing Review Branch 1(MRB1)

Jay Eltermann, Division Director, Division of Manufacturing and Product Quality (DMPQ)

Subject: **Final Review Memo:** Review of BLA submitted by MD Anderson Cord Blood Bank (Houston, TX) to obtain approval for the manufacture, storage, and distribution of minimally manipulated, unrelated allogeneic placental/umbilical Hematopoietic Progenitor Cells, Cord Blood (HPC-Cord)

Action Due Date: 26-June-2018

Recommendation: Approval

Introduction

This review memo serves to document the evaluation and assessment of the applicable Biologics License Application (BLA) review responsibilities by the Division of Manufacturing and Product Quality (DMPQ) in accordance with CBER SOPP 8401.4, *Review Responsibilities for the CMC Section of Biologic License Applications and Supplements*, Effective Date: April 8, 2005 and Guidance for Industry, *Biologics License Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System*, Effective Date June 2014.

The BLA was prepared in eCTD format and submitted through the Agency's Electronic Submissions Gateway, and the cover letter states that precautions were taken to ensure the eCTD is free of computer viruses.

MD Anderson Cord Blood Bank previously filed under BLA 125642 and received a "Refusal to File" letter dated December 16, 2016 which included FDA recommendations for any subsequent submission.

A pre-license inspection was performed February 26 – March 2, 2018. The inspection resulted in a FORM FDA 483 being issued, which contained seven observations.

Table of Contents

I. REVIEW NARRATIVE	3
A. Overview	3
B. Items Reviewed.....	3
II. CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)	4
A. Introduction	4
B. HPC, Cord Blood Description and Characterization	5
C. Manufacturer(s)	5
1. Identification.....	5
a. Manufacturer.....	5
2. Floor Diagram(s)	8
3. Contamination Precautions.....	9
D. Methods of Manufacturing	12
1. SOPs submitted	12
2. Validation	12
a. Process Validation	12
b. Process Simulations (i.e., Media Fills).....	15
3. Flow Charts	17
4. Microbiology	18
5. Control of Aseptic Manipulations	19
a. Precautions.....	19
b. Bioburden/Sterility.....	20
c. In-Process Controls.....	21
6. Batch Records.....	22
7. Critical Reagents and Supplies	22
E. Container Closure System.....	23
F. Shipping	25
G. Environmental Assessment.....	27
III. ESTABLISHMENT DESCRIPTION	27
A. General Information	27
B. Equipment used to process HPC, Cord Blood.....	29
C. Equipment Qualification	32
D. Equipment Maintenance and Calibration	35
E. Flow Diagrams	35
F. Specific Systems	39
1. Water	39
2. Heating, Ventilation, and Air Conditioning (HVAC).....	40
a. Design	40
b. Qualification	42
c. Environmental Quality.....	43
d. Monitoring	44
3. Facility Controls	46
a. Cleaning/sanitization procedures	46
b. Personnel gowning practices.....	47
c. Security / Access control.....	48
d. Environmental Monitoring Program.....	48
4. Computer Systems.....	49
b. Overview	49
c. Change Management.....	50
d. Cord Blood Information System (CBIS).....	51
e. (b) (4)	52

f.	(b) (4)	53
g.	(b) (4)	53
h.	(b) (4)	54
i.	(b) (4)	55
G.	Contamination / Cross-Contamination	55
1.	Equipment Cleaning Procedures and Validation	55
2.	Containment Features	55
IV.	CONCLUSION	56

I. REVIEW NARRATIVE

A. Overview

The HPC-Cord Blood is indicated for use in unrelated hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that is inherited, acquired, or result from myeloablative treatment. The HPC, Cord Blood Injectable Suspension is for intravenous use according to the instructions contained in the Prescribing Information circular.

Each unit contains a minimum of 9×10^8 total nucleated cells with at least 1.25×10^6 viable CD34+ cells at the time of cryopreservation. The exact pre-cryopreservation nucleated cell content of each unit is provided on the container label and accompanying records. Each HPC, Cord Blood Unit that meets safety, purity, potency, and identity specifications is listed in the National Marrow Donor Program (NMDP) Registry. The registry is available for physicians to search and identify a potential donor. The NMDP provides oversight for registry requests, including interaction with MD Anderson to ensure the proper selection, confirmatory testing, and shipping of the HPC, Cord Blood Unit to local, national, and international transplantation centers.

B. Items Reviewed

Section	Subsection
1. Regional	356h Form Cover Letter Request for Categorical Exclusion
2. Common Technical Document Summaries	Introduction – Quality Overall Summary 2.3.P.1 Description and Composition of Drug Product 2.3.P.3 Manufacture 2.3.P.4 Control of Excipients 2.3.P.5 Control of Drug Product 2.3.P.7 Container Closure System 2.3.A.1 Facilities and Equipment
3. Quality	3.2.S.1 General Information 3.2.P.1 Description and Composition of the Drug Product 3.2.P.3.1 Manufacturer(s) 3.2.P.3.3 Description of Manufacturing Process and Process Controls and supporting SOPs 3.2.P.3.4 Control of Critical Steps and Intermediates

	3.2.P.3.5 Process Validation and Evaluation 3.2.P.3.7 Container Closure System 3.2.P.4.1 Specifications
	3.2.A.1 Facilities and Equipment Specific systems (HVAC, Water), facility controls (cleaning, gowning, security, environmental monitoring), contamination control (equipment cleaning, containment features), computer systems (change management, cord blood information system, systems that control critical manufacturing processes, and adjunction systems), equipment (description, calibration, qualification, management), building and equipment monitoring systems, media fill, biological safety cabinets and certifications, shipping (validation, containers, and temperature tracking devices), reagents and supplies (receipt and acceptance, inventory management), diagrams (room classifications, differential pressure cascade), flow diagrams (personnel, product, waste, supplies), location of testing and manufacturing equipment)
3.2.R Regional Information	Batch Records
Amendment 125657/0.6	Responses to DMPQ Information Request (dated 1-10-2018)
Amendment 125657/0.7	Responses to FORM FDA 483 and DMPQ Information Request (dated 1-10-2018) for updated flow diagrams

II. CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

A. Introduction

The cord blood bank is located administratively in the MD Anderson Department of Stem Cell Transplantation and Cellular Therapy of the Division of Cancer Medicine. The Department Chairman is Dr. Richard Champlin, and the Cord Blood Bank Director is Dr. Elizabeth Shpall. Since 2005, the Cord Blood Bank has collected more than 83,000 cord blood donations, banked over 28,000 and released more than 1,700 units for transplantation.

The MD Anderson Cord Blood Bank is registered with the FDA as an establishment of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P's) for Peripheral Blood, Donor Lymphocyte and Cord Blood under 21 CFR 1271. In addition, MD Anderson Cord Blood Bank was accredited by National Marrow Donor Program Cord Blood (NMDP) Network in November 2005 and The Foundation for Accreditation of Cellular Therapy (FACT)-Netcord in March 2006. Reaccreditation by both organizations has been achieved and is current.

B. HPC, Cord Blood Description and Characterization

Hematopoietic Progenitor Cells, Cord Blood (HPC, Cord Blood) is a biologic drug product derived from buffy coat enriched human umbilical cord blood collected from suitable donors. Twenty-five milliliters of HPC, Cord Blood is cryopreserved in a final concentration of 10% DMSO, 1% Dextran 40, and 0.9% Sodium Chloride and stored in liquid nitrogen ($\leq -150^{\circ}\text{C}$). Each HPC, Cord Blood unit contains a minimum of 9×10^8 total nucleated cells and 1.25×10^6 viable CD34+ cells.

Each HPC, Cord Blood unit is packaged in a two-compartment cryobag. The larger compartment contains 80% (20mL) of the injectable suspension and the smaller compartment contains 20% (5mL). The rationale for use of the two-compartment bag is that it allows for the removal of the smaller fraction for further manipulation, such as in-vitro expansion, without thawing the larger bag compartment.

HPC, Cord Blood is placed inside a protective stainless steel canister where it is maintained during cryopreservation, storage and transport. HPC, Cord Blood is shipped frozen using shipping containers (Liquid Nitrogen Dry Shipper) which are designed to maintain the unit at a temperature of $\leq -150^{\circ}\text{C}$ during transport.

C. Manufacturer(s)**1. Identification****a. Manufacturer**

MD Anderson Cord Blood Bank receives cord blood from contracted collection sites (i.e., five in the Houston, TX area and two in Detroit, MI). The processing and storage of HPC, Cord Blood is performed exclusively at the Cord Blood Bank. Testing of the product and associated samples is completed at the Cord Blood Bank or by a CLIA certified contracted testing facility. The table below summarizes the manufacturer, collection sites, and contracted testing facilities, and their responsibility.

Manufacturing/ Testing activities	Inspection / Waiver Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
MANUFACTURER MD Anderson Cord Blood Bank 1841 Old Spanish Trail, Houston, TX 77054 713-563-8000				
Receipt, processing, cryopreservation, storage, testing, registry listing, and distribution of cord blood units <i>Release testing:</i> Sterility and Cell Count	Inspection: YES	YES	YES	FEI: 3010547404 DUNS: 800772139 CAP #: 8727764

COLLECTION SITES				
Ben Taub General Hospital 1530 Taub Loop, Houston, TX 77030 713-873-5374				
Cord Blood Collection Site	Inspection: Not required	NO	NO	
The Woman's Hospital of Texas 7600 Fannin, Houston, TX 77054 713-791-7386				
Cord Blood Collection Site	Inspection: Not required	NO	NO	
Memorial Hermann Southwest Hospital 7600 Beechnut, Houston, TX 77074 713-456-5462				
Cord Blood Collection Site	Inspection: Not required	NO	NO	
St. Joseph Medical Center 1401 St Joseph Parkway, Houston, TX 77002 713-356-7936				
Cord Blood Collection Site	Inspection: Not required	NO	NO	
Memorial Hermann Texas Medical Center 6411 Fannin St., Houston, TX 77030 832-623-4730				
Cord Blood Collection Site	Inspection: Not required	NO	NO	
St. John's Medical Center 22101 Moross Road, Detroit, MI 48236 313-343-7374				
Cord Blood Collection Site	Inspection: Not required	NO	NO	
St. John's Providence 11800 E. Twelve Mile Rd., Detroit, MI 48236 313-343-7374				
Cord Blood Collection Site	Inspection: Not required	NO	NO	

CONTRACT TESTING FACILITIES				
(b) (4)				
(b) (4)	Inspection: Not required	NO	NO	FEI: (b) (4) CLIA ID #: (b) (4) AABB Accreditation
The University of Texas MD Anderson Cancer Center Laboratory Medicine, HLA Lab 6565 MD Anderson Blvd., Room (b) (4), Houston, TX 77030 713-792-2658				
(b) (4)	Inspection: Not required	NO	NO	ASHI #: 04-5-TX-25-1 CLIA ID #: 45D0492022 CAP #: 2108111
(b) (4)				
(b) (4)	Inspection: Not required	NO	NO	CLIA ID #: (b) (4) ASHI #: (b) (4)
(b) (4)				
(b) (4)	Inspection: Not required	NO	NO	FEI: (b) (4)
(b) (4)				
(b) (4)	Inspection: Not required	NO	NO	CLIA ID #: (b) (4) CAP #: (b) (4)

(b) (4)				
(b) (4)	Inspection: Not required	NO	NO	CLIA ID #: (b) (4) CAP #: (b) (4)
(b) (4)				
(b) (4)	Inspection: Not required	NO	NO	CLIA ID #: (b) (4) CAP #: (b) (4)

2. Floor Diagram(s)

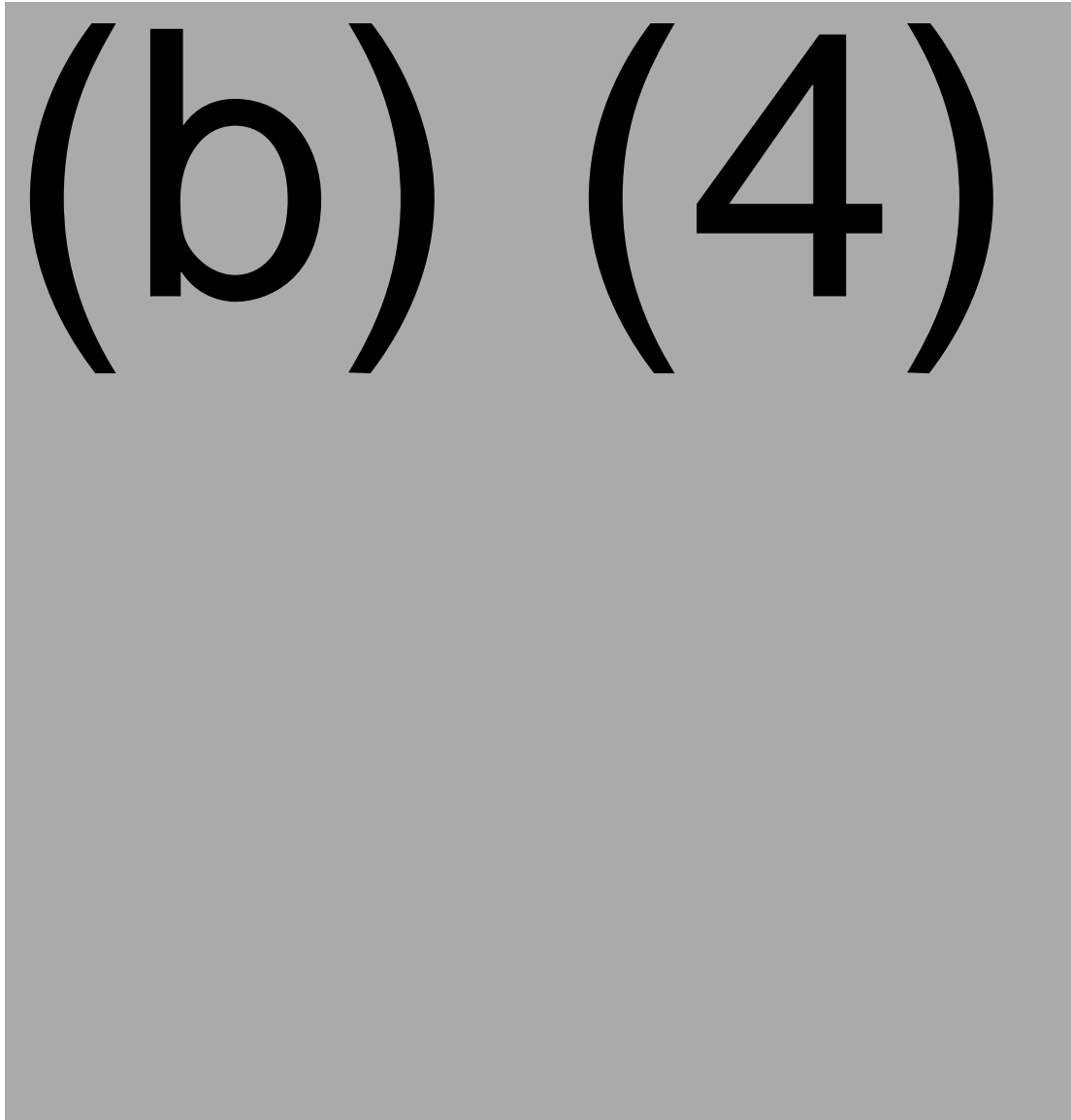
The MD Anderson Cord Blood Bank is located at 1841 Old Spanish Trail in Houston, Texas in the MD Anderson Cancer Center Medical Support Facility (MSF).

The (b) (4) square feet of dedicated space on the first level of the MSF is divided into the following areas: administration, receiving, pre-processing, manufacturing, testing, cryopreservation, long-term storage, and shipping preparation.

Approximately (b) (4) square feet of freezer room space (Room (b) (4)) is dedicated to storage of manufactured hematopoietic progenitor cell (HPC), Cord Blood and the representative and retention samples.

Over (b) (4) square feet of the ISO classified clean room facility is designated for the manufacture and testing of HPC, Cord Blood. The area within the blue dotted boundary lines in Figure 3.2.A.1-1, Cord Blood Bank Floor Plan are the (b) (4) manufacturing and testing suites, and (b) (4) clean corridor, gowning, and supply pass-throughs.

Figure 3.2.A.1-1 Cord Blood Bank Floor Plan (Updated)



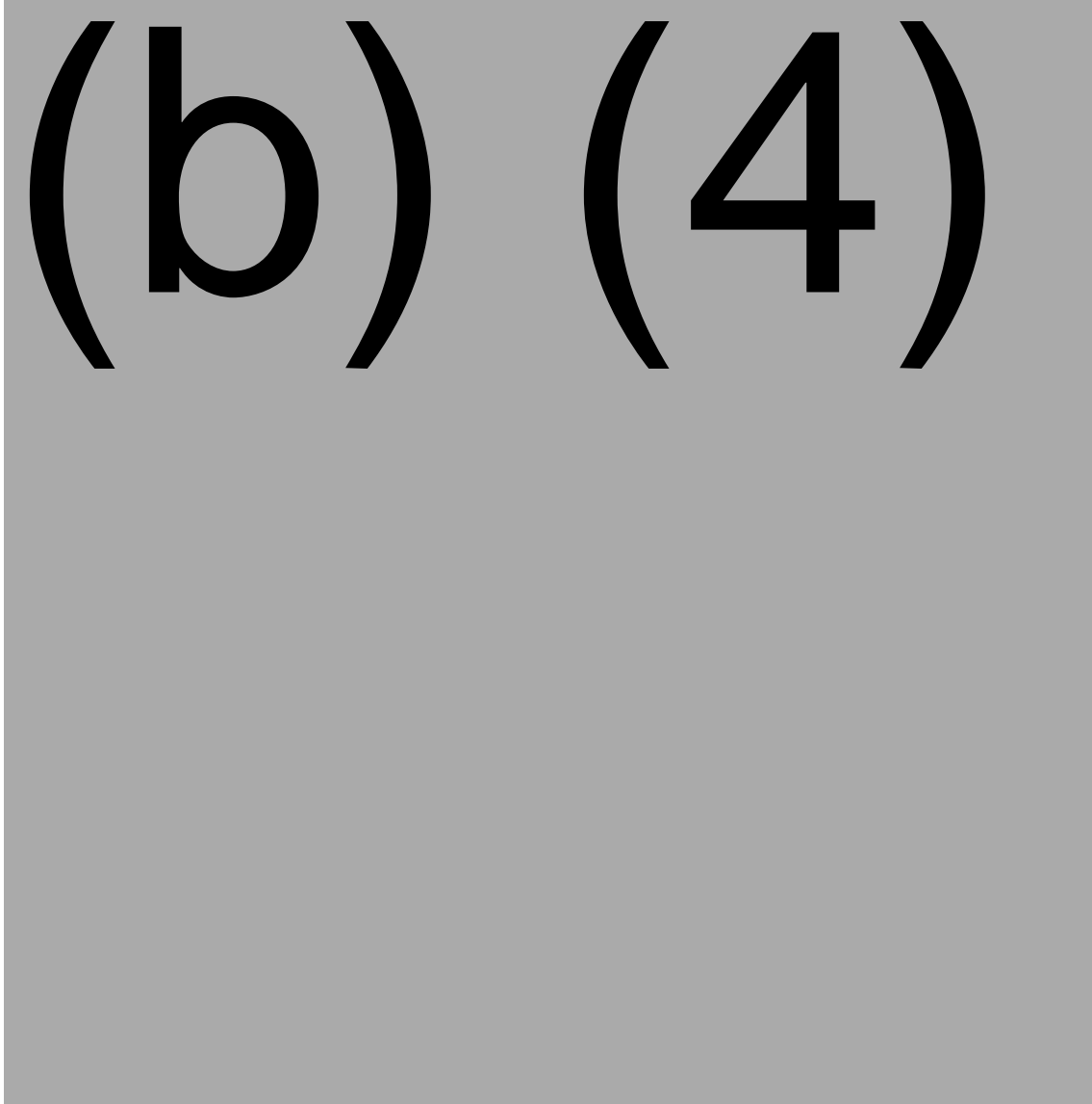
3. Contamination Precautions

Design features

The ISO classified manufacturing and testing laboratories located within MSF were re-commissioned subsequent to renovations in December 2015. The ISO classification of the manufacturing and testing facility is certified (b) (4), with the most recent certification performed in February 2017 by a third party.

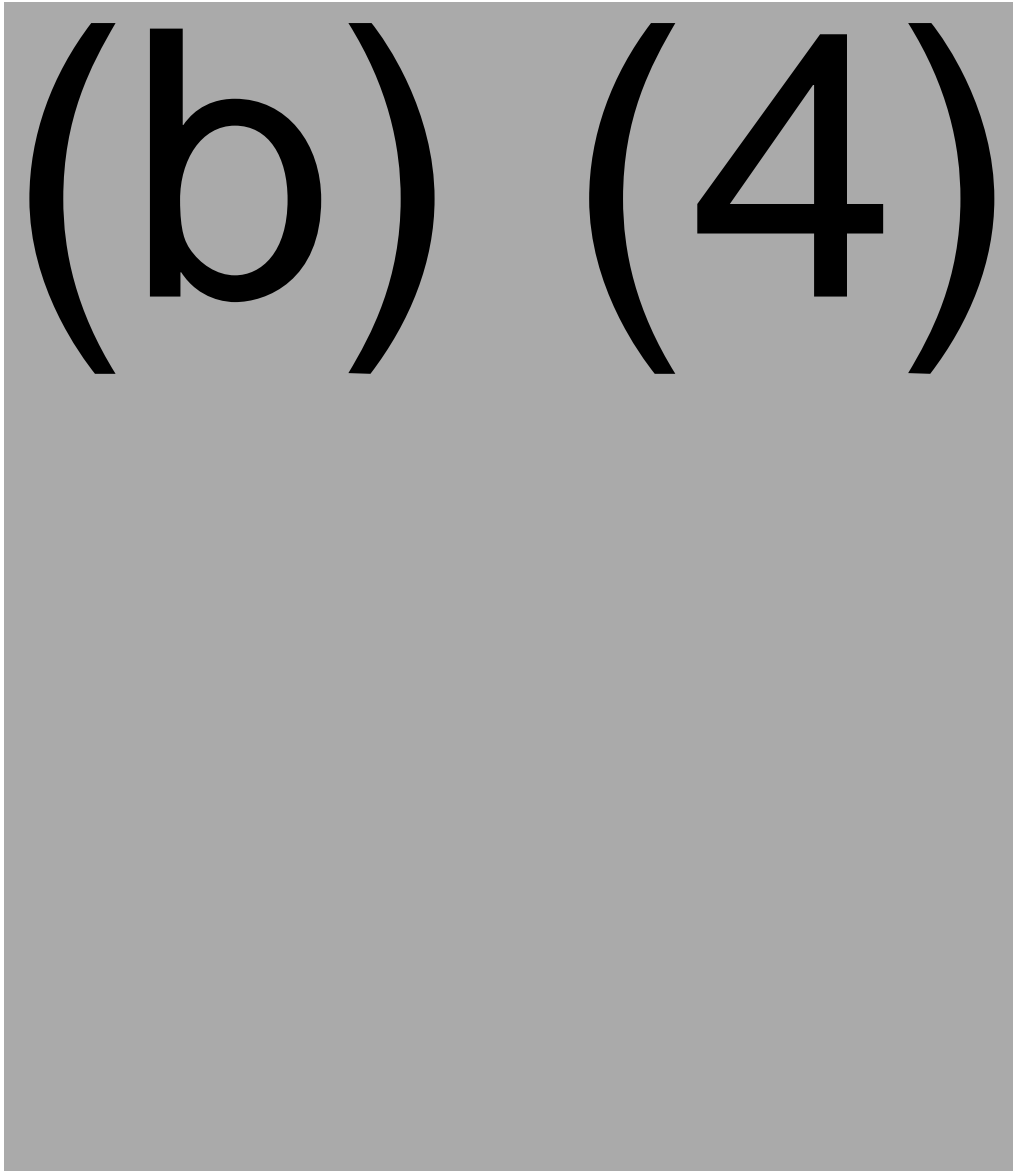
The manufacturing area (Room (b) (4) and testing laboratories (Rooms (b) (4) (b) (4) are designed to meet the requirements for an (b) (4) clean room under ISO standard 14644-1 while the adjacent areas leading to and from the (b) (4) spaces are classified as (b) (4) (Figure 3.2.A.1-2).

Figure 3.2.A.1-2 ISO Classifications by Room (Manufacturing and Testing Laboratories)



(Note: Figure above was copied from Amendment 125657/0.6)

A cascading pressure differential between the (b) (4) manufacturing area and adjacent (b) (4) areas is acceptable for maintaining the integrity of the manufacturing area and products produced within. (Figure 3.2.A.1-3)



Information Request # 1 & 2

1. Please provide the differential pressure for the door between Rooms (b) (4) in Figure 3.2.A.1-3, *Differential Pressure Cascade* (b) (4) Classified Areas.

Reviewer Comment: The differential pressure is reflected in the revised figure above submitted by MD Anderson in Amendment 125657/0.6. The differential pressure of (b) (4)

2. Review of *Environmental Monitoring Schedule and Location* (CBB I 085.055.002) indicates the location of (b) (4) in your facility. Some (b) (4) operate in the same environmental classification (i.e., to/from (b) (4) and other (b) (4) operate in different environmental classifications (i.e., (b) (4) to non-classified area). Please provide a description on

how the (b) (4) operates and how the higher environmental classification area is protected from the introduction of contamination from the lower environmental classification.

Reviewer Comment: The explanation provided by MD Anderson in Amendment 125657/0.6 is acceptable: All (b) (4) are (b) (4) and have interlocking doors. Each (b) (4) is cleaned (b) (4) to each use and at the (b) (4) of the manufacturing day. The defined pressure cascade of the ISO classified manufacturing area is designed to have the airflow move from the higher environmental classification outward to areas of lower environmental classification.

The classified areas of the Cord Blood Bank facility are used specifically for the manufacture, testing, and release of HPC, Cord Blood. There are no other developmental or approved products manufactured or manipulated in the same areas as HPC, Cord Blood.

All surfaces of the facility have been designed to reduce particulates and facilitate cleaning and decontamination. The facility consists of a continuous (b) (4) (b) (4). The walls of the facility are (b) (4) (b) (4). The ceiling of the facility consists of (b) (4) (b) (4).

D. Methods of Manufacturing

1. SOPs submitted

The BLA contained several SOPs, including those pertaining to collection, manufacturing/processing, testing, analytical procedures, disposition of units, computer/electronic collection and storage of information, equipment qualification, process validation, equipment management/maintenance/calibration, shipping, training/competency, facility and equipment cleaning, gowning, and monitoring of the facility. Those SOP relevant to my review were evaluated and incorporated within.

2. Validation

a. Process Validation

MD Anderson executed a process validation to support the cord blood collection, processing, cryopreservation/storage, thawing/cryoprotectant removal, and shipping processes. Prior to executing the validation, the operational status of the facility and biological safety cabinets were verified as in operational condition, the equipment had been qualified and approved for use, and the necessary supplies/reagents utilized during the validation had been ordered, processed, and released for use.

MD Anderson provided a chronological log of cord blood units collected during the execution of the validation. Since MD Anderson receives cord blood from local (Houston metropolitan area) and remote (Detroit, Michigan) collection sites, the log tracked the units received to select validation units covering their five contracted collection sites.

Cord Blood Collection: The chronological log indicates a total of (b) (4) cord blood units were received on April 27, 2016 from five different sites. Each unit was either

transported from a local site or shipped from a remote site to the Cord Blood Bank. Upon receipt, each unit was evaluated against the pre-processing acceptance criteria: time from collection, shipping temperature, visual inspection of the cord blood unit condition and its contents, weight verification, and volume verification. Of the (b) (4) units received, (b) (4) were found to meet the pre-processing acceptance criteria and were released to manufacturing for processing.

Cord Blood Processing: Pre-processing cell counts (i.e., cell recovery, cell dose, viability, CD34 analysis, colony forming unit assay) were performed on the (b) (4) cord blood units. Of the (b) (4) cord blood units, (b) (4) cord blood units collected met the specifications to be released for processing. The (b) (4) cord blood units were processed, resulting in (b) (4) cord blood units that meet the specifications for release for cryopreservation.

Cord Blood Cryopreservation and Storage: All (b) (4) units that were released for cryopreservation were successfully preserved with DMSO and placed in storage within the required time limit.

Cord Blood Thawing and Cryoprotectant Removal: (b) (4) cord blood units were stored for a minimum of (b) (4) hours, and then were used to perform the thawing and washing (i.e., cryoprotectant removal) steps. Table 3.2.P.3.5-4 indicates the post-thaw and wash testing (i.e., cell counts, cell viability, and sterility) met the release criteria for distribution. (Note: Aerobic and anaerobic sterility results were negative.)

Cord Blood Units Shipped: The process validation included results for shipping (b) (4) cord blood units to local (Texas), national (Kansas), and international (Canada, UK) destinations. Shipment summary data in Table 3.2.P.3.5-5 indicates each shipment arrived in expected condition and the shipping temperatures (pre-shipping and upon arrival) met the $\leq -150^{\circ}\text{C}$ specification.

Information Request #3 & 4

3. **Per step 2.4.1 of the *Process Validation Summary Report* (V 013.086.002), you state that the cord blood units will be collected from each local collection site actively collecting at the time of execution of the validation. The supporting validation data indicates five collection sites; however, in your BLA (Table 3.2.P.3.1-1), you list a total of seven collection sites, five in Houston, TX and two in Detroit, MI. Please indicate which collection sites were added subsequent to executing this process validation, and describe how you qualified those collections sites to provide cord blood to your cord blood bank for processing.**

<p>Reviewer Comment: The explanation provided by MD Anderson in Amendment 125657/0.6 is acceptable: At the time of executing the process validation, the collection site at Ben Taub General Hospital was temporarily closed (July 2014 – August 2016) due to staffing shortages and notable reduction of annual births. During the temporary closure, the collection site agreement and IRB approvals for the site were maintained. Prior to re-opening of the site, the collection room was audited against current standards, policies, and procedures. Calibrated equipment</p>
--

and new lots of supplies were delivered, and training of collection staff was performed.

The process validation summary report did not clearly describe the relationship with the cord blood collection program at St. John's Medical Center and St. John's Providence Hospital. Units collected at both St. John's facilities are collected under the same site code (SJDT). The process validation included (b) (4) unit (CBID (b) (4)) collected at St. John's Providence Hospital and (b) (4) units (CBID (b) (4)) collected at St. John's Medical Center.

4. BLA Section 3.2.P.3.5 contains your process validation information which consists of a narrative summary of the process validation, a process validation summary report (CBB V: 013.086.002), and supplemental documents.

A. Our review has determined discrepancies between the narrative summary in the BLA and the process validation summary report. Please provide an explanation for the following:

- 1. Narrative summary states (Cord Blood Processing section) that (b) (4) units met specifications and were released for processing; however, the process validation summary report (section 3.6.2) states that (b) (4) units proceeded to manufacturing. Please note that the supporting data reported in Table 3.2.P.3.5-2 reflects (b) (4) units.**
- 2. Narrative summary (Cord Blood Processing section) states that (b) (4) units met specifications and were released for cryopreservation; the narrative summary (Cryopreservation and Storage section) states that (b) (4) units were cryopreserved. The process validation summary report (section 3.7.2) states that (b) (4) units were cryopreserved. Please note that the supporting data reported in Table 3.2.P.3.5-3 reflects (b) (4) units.**

Reviewer Comment: The explanation provided by MD Anderson in Amendment 125657/0.6 is acceptable: The correct number of cord blood units meeting all pre-processing acceptance criteria was (b) (4) and the correct number of cryopreserved cord blood units was (b) (4). The reporting error does not influence or change the outcomes of the process validation.

B. Regarding *Process Validation Summary Report* (CBB V: 013.086.002),

- 1. Step 2.10.1, states the cord blood units in the validation will be thawed and washed using your (b) (4) method on the (b) (4) however, your procedure (b) (4) *Wash of Thawed Cord Blood Unit* (CBB S 007.025.001) also allows (b) (4) washing for preparing the cord blood unit for infusing to the recipient. Please indicate the wash method used for the (b) (4) thawed and washed units listed in Table 3.2.P.3.5-4.**

Reviewer Comment: The information provided by MD Anderson in Amendment 125657/0.6 is acceptable: All (b) (4) units were washed using the (b) (4) wash procedure CBB S 007.017.003, *Wash of Cord Blood Unit on* (b) (4).

I defer the validation of the (b) (4) wash of thawed units to the product office.

2. Your process validation summary report includes five data summary tables (Tables 4 – 7) listing (b) (4) cord blood units (CBID (b) (4) (b) (4) which you selected as units representing your five collection sites and process.

- a. Please provide your selection criteria for these (b) (4) units, as it appears that these units were selected as validation units retrospectively following the successful completion of the cryopreservation and storage step.

Reviewer Comment: The explanation provided by MD Anderson in Amendment 125657/0.6 is acceptable: The selection criteria were 1) successful cryopreservation of the unit, 2) collection site, 3) race/ethnicity to spare minority units from sacrifice, 4) random selection within the remaining units from each site.

- b. Tables 4 – 7 indicate the collection site using a code. Using the information in Table 3.2.P.3.1-1, we have identified three of the sites to be: MHTM (Memorial Hermann Texas Medical Center), SJMC (St. Joseph Medical Center), and SJDT (St. John's Medical Center). Please provide the site names and addresses for codes SW and TW.

Reviewer Comment: The explanation provided by MD Anderson in Amendment 125657/0.6 is acceptable: Code SW (MHSW) is for the Memorial Hermann Southwest Hospital, Houston, TX and Code TW (TWHT) is for The Woman's Hospital of Texas, Houston TX.

b. Process Simulations (i.e., Media Fills)

Process simulations are used to qualify a new process or changes to the existing manufacturing processes, to initially qualify manufacturing staff, assess competency, and perform periodic requalification of manufacturing staff. Any major change to the manufacturing process requires a minimum of (b) (4) consecutive successful runs, whereas manufacturing staff require participation in (b) (4) successful (b) (4) at completion of training, after (b) (4) months, at (b) (4) months, and (b) (4) thereafter.

Process simulations are scheduled by quality assurance for qualifying a change to the manufacturing process, and by the manufacturing supervisor for assessing staff competency. Manufacturing staff performs the process simulations and quality control staff performs the environmental monitoring before, during, and after the process simulation.

According to *Media Fill – Process and Personnel Qualification* (S 002.019.001), the process simulation consists of environmental qualification of the manufacturing workspace and biological safety cabinet, preparation of a cord blood collection bag with (b) (4) in an (b) (4) certified biological safety cabinet, and processing the collection bag as if it is a cord blood unit that meets all pre- and post-processing requirements, which implies the (b) (4) and cryoprotectant solution (DMSO/Dextran 40) are added to the collection bag. In addition, the process simulation included processing the collection bag using the (b) (4) and the (b) (4). Maximum incubation and hold times were performed for all steps with defined timeframes. The processing simulates the removal of routine in-process test samples (maternal samples, cell counts, sterility); however, the samples are not forwarded for testing except for sterility samples. Upon completion, the final container product bag and seals are (b) (4) and documented on the media fill worksheet.

Sterility test samples are collected throughout the process simulation: pre-processing, post-processing, final product container 80% fraction, and final product container 20% fraction. Each sterility sample is (b) (4)

Acceptance criteria for each process simulation are met when all sterility samples taken from the final product container (i.e., 80% and 20% fractions) exhibit no growth after (b) (4) days. A failure is indicated by detectable growth, on or before (b) (4) days, in one or more of the sterility samples taken from the final product container. If the simulation is being used to qualify a process, all (b) (4) consecutive runs must meet the acceptance criteria. If the simulation is being used to qualify manufacturing personnel, (b) (4) must meet the acceptance criteria. If the process simulation does not pass on the (b) (4) attempt, the individual must be re-trained and re-qualified.

Information Request #5

5. Regarding your process simulation / media fills:

- A. According to *Media Fill – Process and Personnel Qualification* (CBB S 002.19.001), the media-filled collection bag is processed as if it is a cord blood unit that meets pre- and post-processing requirements, and uses the (b) (4). Please clarify if you add the (b) (4) to the collection bag and DMSO/Dextran40 to the final product container during your media fill.

Reviewer Comment: The response to the Information Request was received after the pre-license inspection was performed. During the pre-license inspection, it was confirmed that (b) (4) DMSO/Dextran 40 are added to the collection bag during the medial fill.

The information provided by MD Anderson in Amendment 125657/0.6 is acceptable: (b) (4) DMSO are added to the collection bag during the current Media Fill to simulate the normal aseptic process. Based on discussion during the pre-license inspection and corrective action for FORM FDA 483 Observation #6, the media fill procedure will be updated to simulate the

addition of the (b) (4) DMSO using media, of equivalent volumes, and sterile weld connections as performed during routine manufacturing of the cord blood units.

The revised procedure provided in Amendment 125657/0.7 was found acceptable.

- B. During your media fills, you collect sterility samples at (b) (4) Collected samples from all (b) (4) collection points are inoculated and incubated. Your media fill acceptance criteria is based on sterility results from the final product container. Please provide a justification for your acceptance criteria being based solely on the sterility test results from the final product container. In addition, please explain what actions you would take if your sterility test results from the pre- and post-processing samples exhibited growth.

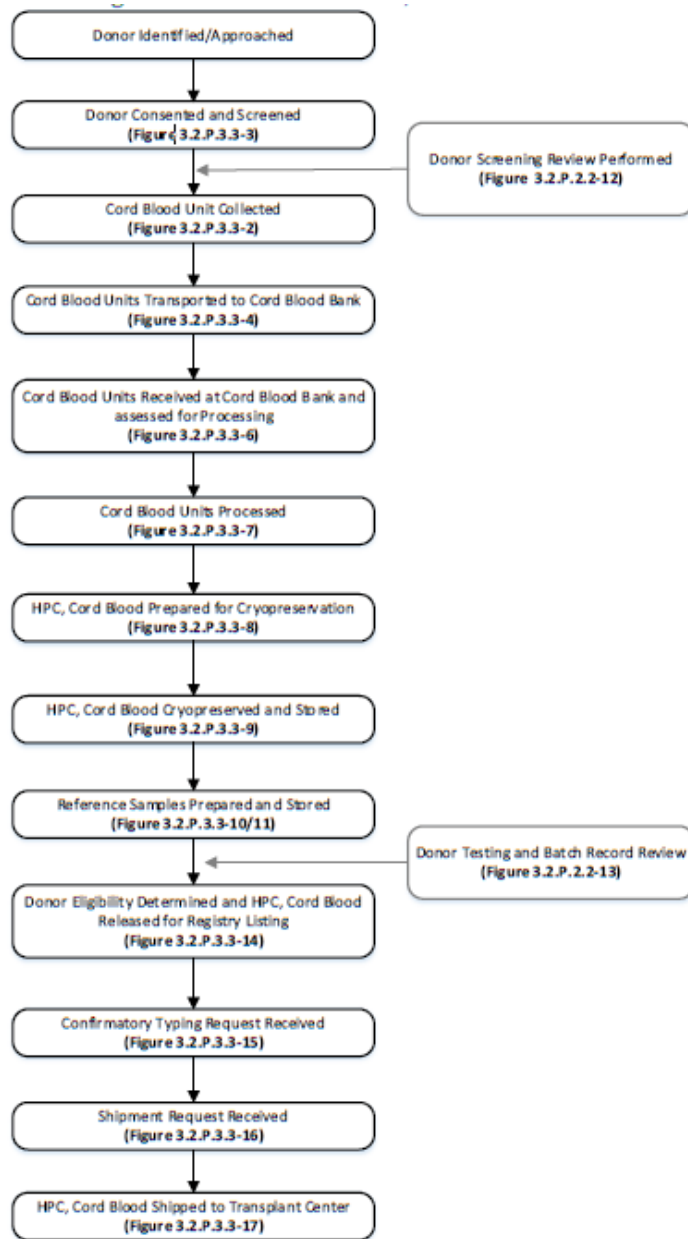
Reviewer Comment: The information provided from MD Anderson submitted in Amendment 125657/0.6 is acceptable: The revised procedure, CBB S 002.019.003 *Media Fill – Process and Personnel Qualification* includes updated acceptance criteria to require all sterility samples taken must not exhibit growth.

The revised procedure was provided in Amendment 125657/0.7 and found acceptable.

3. Flow Charts

The BLA included several flow charts, which provided a visual representation of the manufacturing process. The flow charts were reviewed to assess product transfer methods, hold times, and in-process controls. Figure 2.3.P.3 (below) provides a high-level overview of the HPC, Cord Blood manufacturing process defines the process, and references the subsequent flow charts.

Figure 2.3.P.3



(Figure 2.3.P.3 copied from page 2, Section 2.3.P.3 Manufacture, of the BLA)

4. Microbiology

MD Anderson does not sterilize any equipment or supplies that are used for the collection, manufacturing, and processing of the cord blood unit. Critical supplies / reagents that come in contact with the product are supplied sterile, disposable, single-use items. The sterilization methods are summarized below:

- **Cord Blood Collection Unit:** Sterilization process validated per ANSI/AAMI/ISO 17665, Sterilization of Health Care Products – Moist Heat.

- **(b) (4) 0.9% Sodium Chloride Injection):** Sterility must meet requirements of parametric release and meet endotoxin specification of not more than (b) (4).
- **DMSO/Dextran40 in 0.9% saline: (b) (4)**
(b) (4) The solution is aseptically filled in a US facility which is licensed to fill pharmaceuticals. Filled syringes must pass (b) (4) sterility testing and meet endotoxin specification of (b) (4).
- **BioSafe Cryobag:** Sterilized by (b) (4) per ISO 11135-1:2007.

5. Control of Aseptic Manipulations

a. Precautions

Control of aseptic manipulations is achieved by various precautions to control contamination, and it begins with in-utero or ex-utero collection of the cord blood.

Cord blood collection precautions include:

- Use of (b) (4) collection bags which are sterile and approved for use by FDA.
- Collection takes place in the delivery room for vaginal and C-section deliveries or in dedicated collection room for ex-utero collections by trained healthcare staff using aseptic techniques.
- The umbilical cord is disinfected with an approved tissue cleaning solution (b) (4)
- The collection needle cover is removed prior to insertion to eliminate any issues with the introduction of contamination during the collection process.
- Post-collection area is cleaned and sanitized, and all biohazardous material is appropriately disposed.
- The single-use collection bag is clamped closed after the cord blood has stopped flowing into the collection bag, and transported to the manufacturing site for receipt and pre-processing assessment.

Manufacturing site precautions include:

- Pre-processing assessment and check-in of cord blood is performed in an (b) (4) classified environment.
- Manufacturing is performed using a functionally closed system within an (b) (4) classified environment, and use of sterile weld connections for all manipulations.
- Only one unit is processed at a time.
- Appropriate measures are in place to address any breach of the cord blood unit.
- Equipment is cleaned prior to each use.
- Established procedures for cleaning the surfaces, floors, walls, etc. of the manufacturing and testing areas.
- The use of process simulations, i.e., media fills; to qualify a new or changed process, operators, and assesses the aseptic technique used in the manufacturing processes to ensure it does not cause or contribute any contamination to the cord blood unit.

- Environmental monitoring program includes monitoring of viable and nonviable airborne particulates and surfaces.

Aseptic transfer identified

(b) (4)

(b) (4)

Information Request #6

6. Your manufacturing process includes the (b) (4)

Reviewer Comment: The information provided by MD Anderson in Amendment 125657/0.6 is acceptable: Validation V 013.039.001 showed that the transferred (b) (4) maintained sterility up to (b) (4) days. Validation V 013.070.001 (b) (4). The Cord Blood Bank is in the process of executing an addendum VA1 013.070.001 to demonstrate that sterility of the transferred (b) (4) is maintained (b) (4) expiration date. The supporting data was submitted to the Agency. The firm does not intend to extend the expiration date beyond (b) (4) days.

b. Bioburden/Sterility

Sterility testing is performed using a surrogate test sample, i.e., the red cells resulting from the (b) (4)

The use of a surrogate sample for sterility testing is common, as previously approved cord blood BLA's have used either red cells, plasma, or red cells and plasma for microbiological testing, as the cord blood volume is not sufficient to allow the reduction of the cord blood volume by the quantity (b) (4) used to perform the sterility test, and still have sufficient quantity for transplantation purposes. The product office has

evaluated the analytical method validation as well as the blood component(s) used as the surrogate test sample.

The microbiological testing uses the (b) (4) designed for detecting bacteria, yeast, and fungi present in blood specimens. Therefore, the use of the surrogate red cell sample for testing is suitable. (b) (4) culture bottles are inoculated, incubated, and interpreted. Any positive results are sent out for further analysis and the associated cord blood unit is discarded.

c. In-Process Controls

MD Anderson has established in-process controls to ensure a consistent and reproducible manufacturing process. In addition, the Cord Blood Bank has defined (b) (4) stages of manufacturing as critical “release” points. These “release” points are used to determine whether the cord blood unit is suitable to proceed to the next stage of manufacturing or be released. The following table contains in-process controls and product specifications that have been determined to ensure or maintain the safety, purity, and potency of HPC, Cord Blood units.

In-Process Control	Limit	Justification
DMSO addition	(b) (4)	(4)
Final freeze bag integrity		
Overwrap Integrity		
Label verification		
Start of Cryopreservation		
Freeze Curve		
Visual inspection of cryopreserved product		
Verification post thaw results meet acceptance criteria		

6. Batch Records

An executed batch record for a cord blood unit consists of documentation pertaining to: donor consent, positive identification of the birth mother and the cord blood unit, donor screening, donor testing and results, final donor eligibility determination, and review and release to the NMDP searchable inventory. The executed batch record also includes processing and testing documentation for manufacturing, testing, and storage of the HPC, Cord Blood. In addition, the executed batch record includes documentation of the manufacturing and testing steps, as well as the equipment and supplies that were used.

The executed batch record was provided for HPC, Cord Blood unit (b) (4), which is representative of the manufacturing process and process controls described in the BLA. The executed batch record was redacted for personal identifiable information, demographics, and confidential medical information. HPC, Cord Blood batch records do not conform to the typical batch record design used by biological drug product manufacturers. The batch record consists of printouts of electronic records, which are manually reviewed and verified, followed by quality assurance approval. Therefore, documentation contained in the batch record meets the definition of electronic records and electronic signatures per 21 CFR Part 11.

Table 3.2.R.1-1 describes the content and location for the executed batch record for HPC, Cord Blood unit (b) (4). I reviewed the following sections:

- Final Review for Listing, pages 1 -3
- Sterility Report, pages 33 – 34
- Cryopreserved Unit Summary Report, pages 37- 38
- Freezing and Storage Record, page 39
- Maternal Blood Sample Processing, pages 44 – 46
- Processing Times Log, page 59
- Cord Blood Cryopreservation Using the (b) (4), pages 60 – 62
- (b) (4) Procedure Summary, page 63
- Cord Blood Processing on the (b) (4), pages 64 -68
- (b) (4) Protocol Summary, page 69
- Cord Blood Check-in and Pre-processing Acceptance, pages 74 - 78

7. Critical Reagents and Supplies

SOP P 052.002.003, *Reagents and Supplies for Collection, Banking, and Release for Administration of Cord Blood* defines critical reagents and supplies as those that come in direct contact with cord blood. The critical reagents and supplies are commercially available from approved vendors, provided sterile, single-use, approved for human use (when possible), are subject to purchasing controls, and summarized below.

Reagent / Supply	Function
Dimethyl sulfoxide (DMSO)	Dimethyl sulfoxide is used to protect biologic tissues from damage that occurs as a result of the formation of ice crystals during the cryopreservation process.

0.9% Sodium Chloride Solution	0.9% Sodium Chloride Solution is used to dilute the DMSO/Dextran cryopreservation media.
Dextran 40	Dextran 40 is used to protect biologic tissues from damage that occurs as a result of the formation of ice crystals during the cryopreservation process.
Citrate Phosphate Dextrose (CPD)	Citrate Phosphate Dextrose (CPD) is the anticoagulant supplied as part of the (b) (4) intended to prevent the natural clotting process found in human blood products including HPC, Cord Blood.
(b) (4)	(b) (4)
(b) (4) Cryobag	Primary container for cryopreservation, storage and transport of product.
Canister, stainless steel	Secondary container for cryopreservation, storage and transport of product.

E. Container Closure System

MD Anderson provided information of the containers and closure systems used for the collection, manufacture, cryopreservation, and storage of HPC, Cord Blood.

Collection

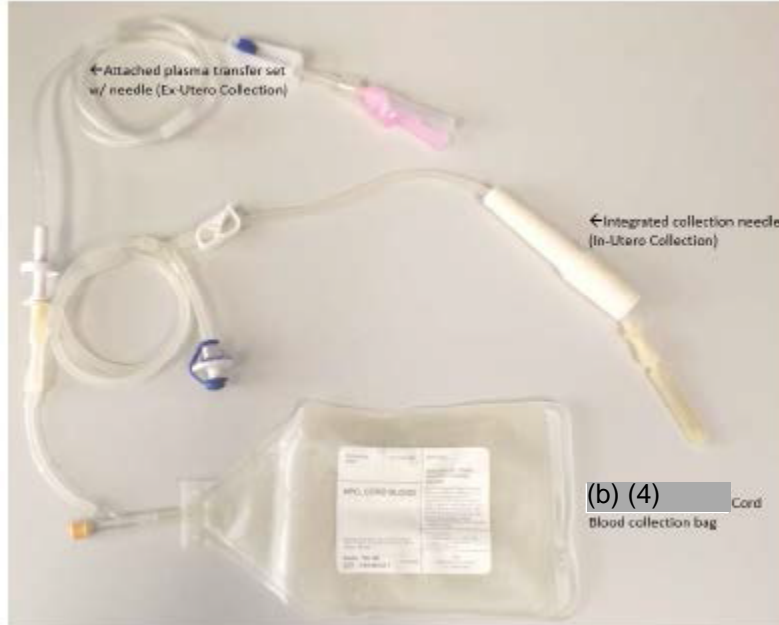
A Cord Blood Collection Kit is used for collecting up to (b) (4) mL of umbilical cord blood and contains (b) (4) mL of anticoagulant (CPD, Citrate Phosphate Dextrose). The kit is assembled and provided by MD Anderson to the collection sites. The kit includes a collection bag (b) (4) Part (b) (4) and plasma transfer set (b) (4) Part # (b) (4) provided as sterile, single-use components. The BLA included a Certificate of Analysis for the collection bag and transfer set.

The collection bag is FDA approved under NDA: BN800222. The bag includes a sterile air vent permitting cord blood to drain into the collection bag, minimizing the risk of contamination by the surrounding environment. The collection bag is supplied with an integrated collection needle used for ex-utero cord blood collection. The transfer set includes a port spike and needle, which is aseptically attached via a sterile docking connection to the collection bag only when attempting to perform an in-utero cord blood collection. The port spike connection maintains the sterility of the collection bag.

After completing the cord blood collection, metal clips are attached to each tubing line connected to the collection bag, crimped closed using a hand-operated crimping device, placed in a zip-seal bag, and stored awaiting transport.

The following image shows the (b) (4) Cord Blood collection bag with both the plasma transfer set with needle and the integrated collection needle, attached to the collection bag.

Cord Blood Collection Kit with Attached Plasma Transfer Set



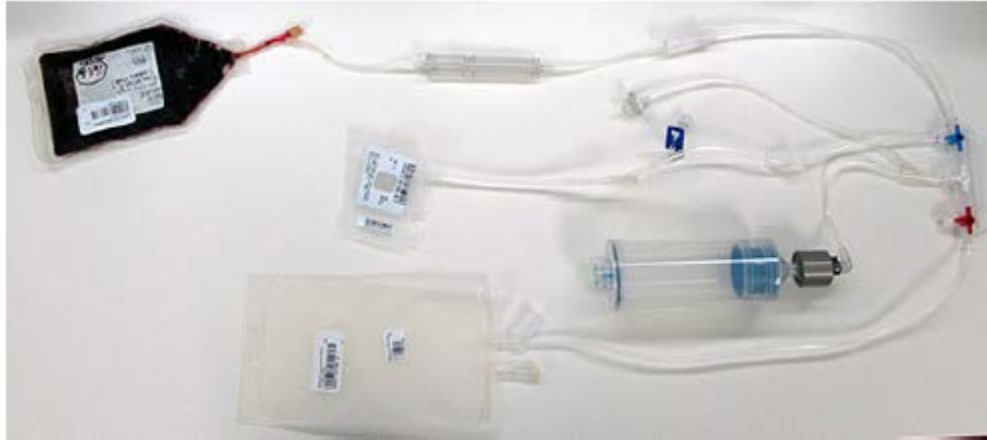
(Note: Image above was copied from page 6, Section 3.2.P.3.3 of the BLA).

Manufacture

The cord blood collection bag serves as the container closure system during the processing in the (b) (4) manufacturing area. The addition of Hydroxyethyl starch (HES) is performed using sterile connect devices and syringes. The collection bag is processed using the S(b) (4)

The following image shows a cord blood unit connected via sterile connection to the (b) (4) (b) (4) consists of tubing with valves to control the flow of blood components to either the red cell bag, the plasma bag, or the buffy coat bag. This assembly is placed into the (b) (4) centrifuge for automated separation of the various blood components. Upon completion of the automated procedure, the plasma, red blood cell, and buffy coat bag are sealed using a tubing heat sealer and removed from the remainder of the (b) (4), which is discarded. A syringe is connected to the buffy coat bag using a sterile connection device, and a small aliquot (b) (4) is removed for cell enumeration and characterization. The buffy coat is stored at (b) (4), pending cryopreservation. Buffy coat units meeting all the required specifications are released for cryopreservation.

Cord Blood Unit with Sterile Connection to (b) (4)



(Note: Image above was copied from page 21, Section 3.2.P.3.3 of the BLA).

Cryopreservation and Storage

The cryobag containing the buffy coat has a syringe containing the premixed cryoprotectant solution connected to the fill line of the cryobag. The connection is made using a tube welder (b) (4) to make a sterile connection. The weld is inspected. The cryoprotectant is added to the cryobag using a syringe (b) (4) while the cryobag is mixed and cooled using an automated mixing/cooling platform (b) (4). After the transfer of the cryoprotectant is complete, the excess air is removed from the tubing line using the attached syringe. A heat sealer (b) (4) is used to create three equal segments on the tubing line. (Note: During the PLI, the product office discovered that four segments were being created. The firm submitted an amendment for this change, which is applicable to the product office).

The cryobag is placed in a protective overwrap bag (BioSafe) and (b) (4) using a heat sealer (b) (4). The seal is inspected. The overwrapped cryobag is placed in a canister and undergoes controlled-rate freezing using the (b) (4).

F. Shipping

MD Anderson provided details and flow charts for the shipping process of cord blood units collected by the collection sites (local and remote locations), and shipping of the frozen HPC-Cord Blood units in liquid nitrogen dry shippers to the transplant centers.

From the Collection Site to the Cord Blood Bank

Cord blood units and maternal blood samples collected at the two remote and five local sites, are stored in clean totes/containers on secure, temperature and humidity monitored collection rooms until they are transported to the Cord Blood Bank for processing. Transport of the cord blood units and maternal blood samples to the Cord Blood Bank occurs daily from the seven collection sites. The temperature inside the transport container is continuously monitored during transport. The BLA included detailed descriptions, procedures, and process flow charts for local and remote site storage and transport. The Product Office reviewer took the lead for reviewing the storage and

transport process used by the collection sites, including training, temperature monitoring and measuring devices, transport methods, and chain of custody. The release of cord blood units to processing requires the time from collection to be (b) (4) hours post-collection.

From the Cord Blood Bank to the Transplant Center

Prior to any shipment to the transplant center, the Cord Blood Bank performs a complete review of the internal HPC, Cord Blood unit file to ensure completeness, including confirmatory typing and internal unit assessment results, that confirms suitability for release for distribution.

(b) (4) initiates the shipment workflow application to begin the tracking process. The preparation for shipping follows two tracks: preparation of the Liquid Nitrogen Dry Shippers and review of the shipment packet (i.e., records pertaining to the specific unit) by cord blood staff and approved by quality assurance. Only one HPC, Cord Blood unit can be shipped per dry shipper.

All dry shippers are qualified initially and re-qualified (b) (4) for use in shipping cord blood units. The initial and re-qualification verifies the shipper can maintain the minimum validated shipping interval (MVSII). Three different brands and sizes of dry shippers have been validated for use in shipping cord blood:

- (b) (4)

The dry shipper consists of a vacuum jacketed aluminum dewar containing adsorbent material which retains liquid nitrogen. Preparation for shipping a cord blood unit consists of: 1) selecting the appropriate shipper based on the estimated shipping interval, 2) clean and inspect the dry shipper, 3) primary charging of the dry shipper with liquid nitrogen, 4) secondary charging of the dry shipper, if applicable, 5) removal of excess liquid nitrogen after required hold time, and 6) weigh the dry shipper (must weigh between (b) (4)

The shipment data logger is configured with shipment specific information, initiated, and installed in the shipper lid, where the pre-loading temperature of $\leq -150^{\circ}\text{C}$ is confirmed. The HPC-Cord Blood unit is removed from (b) (4) storage by scanning the barcoded unit number located on the shipment report. The unit is placed in a stainless steel canister and the stainless steel canister is placed in a temperature monitored vessel capable of maintaining $\leq -150^{\circ}\text{C}$. The identity of the unit is verified (b) (4) by (b) (4) separate technicians and placed into the prepared dry shipper. The inner lid of the dry shipper is secured, and the shipment packet is secured to the inside of the outer lid of the dry shipper. Shipments are released to couriers only upon verification of the shipment tracking number at the time of courier pick-up. Transplant centers return the shipment data logger to MD Anderson for downloading and review of the shipment data. For qualification of dry shippers and data loggers, refer to Equipment Qualification Section III.C for details.

G. Environmental Assessment

MD Anderson Cord Blood Bank requested a categorical exclusion from preparing an environmental assessment pursuant to 21 CFR 25.31(c), which applies to a biological product containing substances that occur naturally in the environment when the introduction of the product does not alter significantly the concentration or distribution of the substance, its metabolites or degradation products in the environment. The request for categorical exclusion is justified because the product meets the exclusion criteria in 21 CFR Part 25; however, there is no statement that covers 21 CFR 25.15(d).

Information Request #7

7. You have requested a categorical exclusion from preparing an environment assessment pursuant to 21CFR 25.31(c). This request also needs to include the information required by 21CFR 25.15(d). Please provide the necessary statement to support your categorical exclusion request.

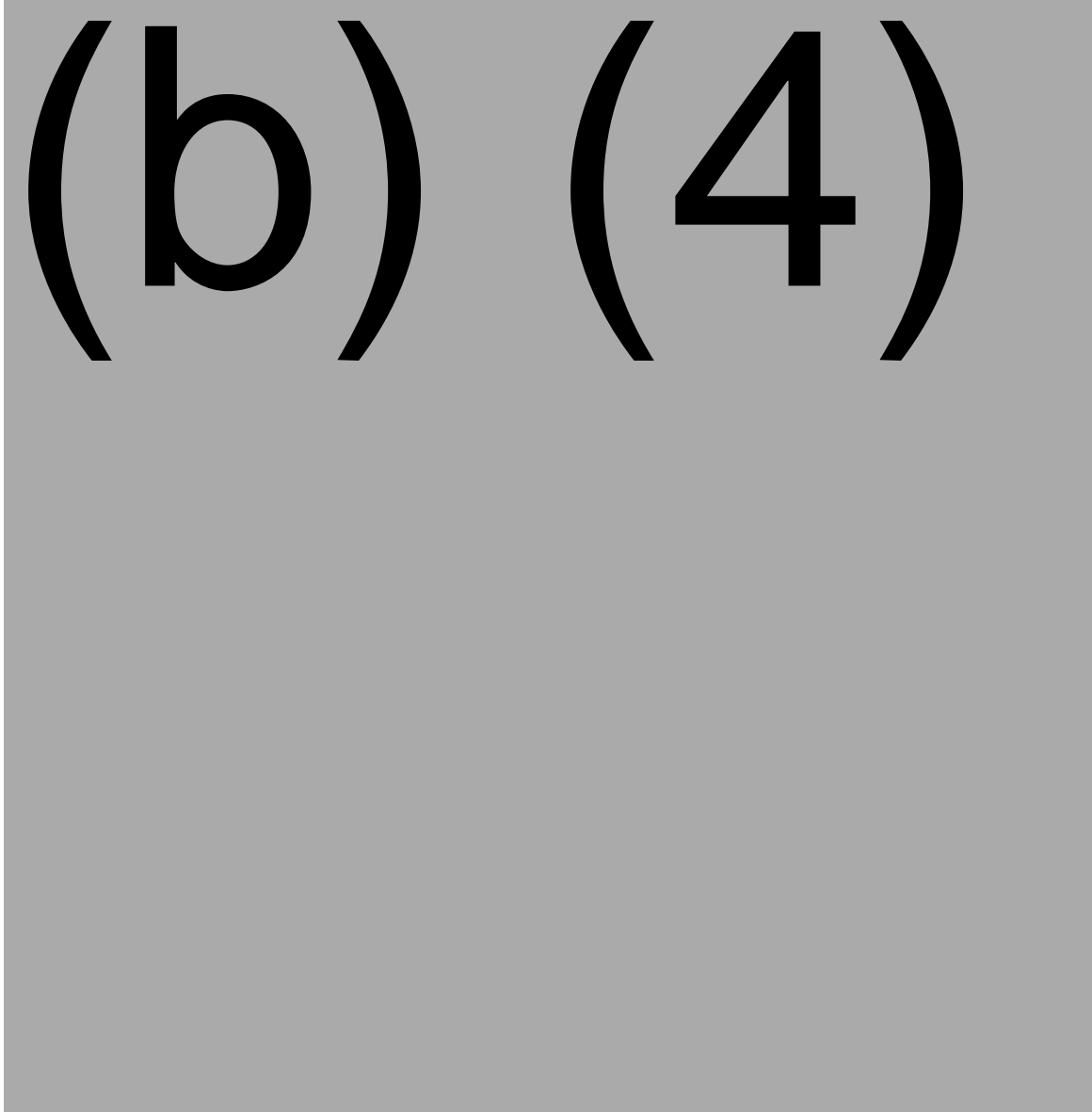
Reviewer Comment: The revised categorical exclusion request provided by MD Anderson in Amendment 125657/0.6 is acceptable and reads as follows: MD Anderson Cord Blood Bank formally requests a categorical exclusion from the preparation of an environmental impact statement for the HPC, Cord Blood product as the substance/product occurs naturally in the environment [21 CFR 25.31(c)]. The manufacturing process does not alter significantly the concentration or distribution of the substance, its metabolites or degradation products in the environment. To MD Anderson Cord Blood Bank's knowledge, no extraordinary circumstances exist.

III. ESTABLISHMENT DESCRIPTION

A. General Information

Over (b) (4) square feet of the ISO classified clean room facility is designated for the manufacture and testing of HPC, Cord Blood. The area within the blue dotted boundary lines in Figure 3.2.A.1-1, Cord Blood Bank Floor Plan are the (b) (4) classified manufacturing and testing suites, and the (b) (4) classified clean corridor, gowning, and supply pass-throughs.

Figure 3.2.A.1-1 Cord Blood Bank Floor Plan (Updated)



Information Request #8 & 9

8. The review of Figures 3.2.A.1-1 (*Cord Blood Bank Floor Plan*), 3.2.A.1-2 (*ISO Classification by Room*), 3.2.A.1-3 (*Differential Pressure Cascade*) and Tables 3.2.A.1-1 *Cord Blood Bank Blood Room Detail (Non-Classified Space)* and 3.2.A.1-2 *Cord Blood Bank Room Detail (ISO Classified Space)* has identified discrepancies and missing information. Please review all five documents, update as necessary, and resubmit. The following issues are examples of the discrepancies noted in the reviewed documentation in your BLA:
 - A. In Figures 3.2.A.1-1 and 3.2.A.1.2 it appears that the room/laboratory adjacent to the Manufacturing lab (Room (b) (4)) is mislabeled as Room (b) (4) instead of (b) (4). (Note: Room (b) (4) is the Lab Exit according to the floor plan and description listed in Table 3.2.A.1-2).

- B. Figure 3.2.A.1-1 includes rooms labeled as (b) (4) however, descriptions of these rooms are not listed in Table 3.2.A.1-1.
- C. Table 3.2.A.1-1 includes Room (b) (4); however, this room cannot be found in Figure 3.2.A.1-1.
- D. Table 3.2.A.1-1 includes Room (b) (4) (Corridor); however, this room cannot be found in Figure 3.2.A.1-1.

Reviewer Comment: The updated figures and tables provided by MD Anderson in Amendment 125657/0.7 are acceptable.

9. Please clarify if the freezer room (i.e., where cryopreserved HPC, Cord Blood is stored) is Room (b) (4)

Reviewer Comment: The information provided by MD Anderson in Amendment 125657/0.6 is acceptable: the reference to Room (b) (4) has been removed.

The classified areas of the Cord Blood Bank facility are used specifically for the manufacture, testing, and release of HPC, Cord Blood. There are no other developmental or approved products manufactured or manipulated in the same areas as HPC, Cord Blood.

B. Equipment used to process HPC, Cord Blood

The following table summarizes the equipment, its location, and purpose in the manufacture, storage, and distribution of HPC, Cord Blood.

Equipment Description	Room Number	Purpose
(b) (4)	(b) (4)	
Biological Safety Cabinet		
(b) (4)		
(b) (4)		
Liquid Nitrogen Dry Shipper	(b) (4)	Maintains temperature (≤ -150 °C) and provides protection of HPC, Cord Blood units during shipment
Refrigerator	(b) (4)	
(b) (4)		

Sterile Connection Device	(b) (4)	Sterile connection of kits and tubing during manufacturing
Syringe (b) (4)	(b) (4)	Control rate of DMSO addition
Tube Sealer	(b) (4)	Sterile sealing of bags, fill lines, and processing kits

(b) (4)

The manufacturing room (b) (4) contains sterile connection devices and tubing heat sealers on the (b) (4) of the room, (b) (4) biological safety cabinets are located on the (b) (4) of the room, (b) (4) refrigerator, (b) (4) and (b) (4) syringe (b) (4) on the west side of the room, and (b) (4) sealers on the (b) (4) end of the room.

The following table summarizes the equipment, its location, and purpose for testing of HPC, Cord Blood.

Equipment Description	Room Number	Purpose
(b) (4)	(b) (4)	(b) (4)

Balance	(b) (4)	Weight/volume determination of pre-processing cord blood unit
Biological Safety Cabinet	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Cell counter	(b) (4)	Cell enumeration
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Flow cytometer	(b) (4)	CD34+ enumeration and viability determination
Incubator	(b) (4)	(b) (4)
Microscope	(b) (4)	(b) (4)

(b) (4)

Testing lab, room (b) (4) is used for pre-and post-processing product characterization. Room (b) (4) contains (b) (4) cell counter on a (b) (4) on the (b) (4) side of the room, (b) (4) balances on the (b) (4) in the (b) (4) of the room, and (b) (4) biological safety cabinet on the (b) (4) side of the room. Testing lab, room (b) (4) is used for flow cytometric analysis/enumeration of HPC, Cord Blood. Room (b) (4) contains a (b) (4) on

the (b) (4) side of the room. Testing lab, room (b) (4) is used for performing Colony Forming Units (CFU) assays, and contains (b) (4) biological safety cabinets and (b) (4) incubators on the (b) (4) side of the room, and (b) (4) microscopes on the (b) (4) side of the room.

Adjacent (b) (4) areas to the manufacturing and testing suites are summarized in the following table.

Room	Name	Purpose
(b) (4)	Clean corridor	Corridor to manufacturing and testing labs
	Gowning Room	Secure access entrance to clean room processing facility. Primary gowning room for entrance to ISO classified facility.
	Dressing Room	Changing room: street clothes to scrubs
	Manufacturing lab gowning	Secondary gowning
	Supply pass-through	Released supply storage
	Testing lab gowning	Secondary gowning
	Lab Exit	Exit from manufacturing and testing labs

C. Equipment Qualification




(b) (4)

The installation and operational qualification included assembly, functional testing, alignment checks, software loading, verify freeze profile, maintenance schedule, and current date and time. The performance qualification included testing of the remote alarm, successful storage and retrieval actions in (b) (4). All (b) (4) qualifications met specifications.

The CBB validated the (b) (4) system as described in Summary Report: *Validation of the Cord Blood Bank Collections, Manufacturing, Testing, Cryopreservation, Storage, and Shipping Process*, V:013.086.002. The (b) (4) equipment utilized during the process validation verified that the equipment was installed properly and operated as required. All (b) (4) cord blood units included in the validation were successfully cryopreserved and stored. For more details, refer to Process Validation in section II.D.2.a.

(b) (4)



(b) (4)



Following successful IQ and QO, the CBB validated the (b) (4) system as described in *Summary Report: Validation of the Cord Blood Bank Collections, Manufacturing, Testing, Cryopreservation, Storage, and Shipping Process, V:013.086.002*.

The (b) (4) equipment (including the computer, software, peripherals) utilized during the process validation verified that the equipment was installed properly and operated as required. All (b) (4) thawed and washed units yielded acceptable sterility results. For more details, refer to Process Validation in section II.D.2.a.

(b) (4)



The document finds the IQ and OQ were specifications and no functionality issues were identified. The report states the unit is suitable for GMP use.

(b) (4)

(b) (4)

Note: Equipment qualification of testing equipment is deferred to the product office.

D. Equipment Maintenance and Calibration

Reviewed *Equipment Management* (S 002.016.002) which addresses the repair, recall, and retirement of equipment used for the manufacture and testing of the cord blood units.

Reviewed *Master Calibration* (S 011.025.002) which describes the equipment qualification, calibration, and preventive maintenance requirements for all equipment used by MD Anderson. The table below summarizes the maintenance requirements listed in the referenced SOP. (Note: (b) (4))

Equipment	Maintenance and Frequency
(b) (4)	(b) (4)

E. Flow Diagrams

The BLA contained diagrams depicting the flow of personnel, product, materials, and waste, as it enters, progresses through, and exits the facility, in a (b) (4) manner. Review of the flow diagrams found no concerns, other than these diagrams have the same discrepancies with room numbers, as previously identified.

(b) (4)

Information Request #10

10. Flow diagrams for personnel, product, materials, and waste include incorrect room or duplicated room numbers. (Similar issues as in Information Request #8). Please correct all four flow diagrams (Figures 3.2.A.1-5 through 3.2.A.1-8) and resubmit.

<p>Reviewer Comment: The revised personnel, product, materials, and waste flow diagrams provided in Amendment 125657/0.6 are acceptable.</p>

F. Specific Systems

1. Water

MD Anderson Cord Blood Bank does not generate or purchase water for production of HPC, Cord Blood. There is no indication whether any potable water is used in cleaning of equipment or the facility, either for diluting the cleaning agent or as a rinsing agent.

Information Request #11

11. Please indicate if any water (i.e., potable) is used during the cleaning of equipment or the facility, in rinsing the surface or for diluting the cleaning agent.

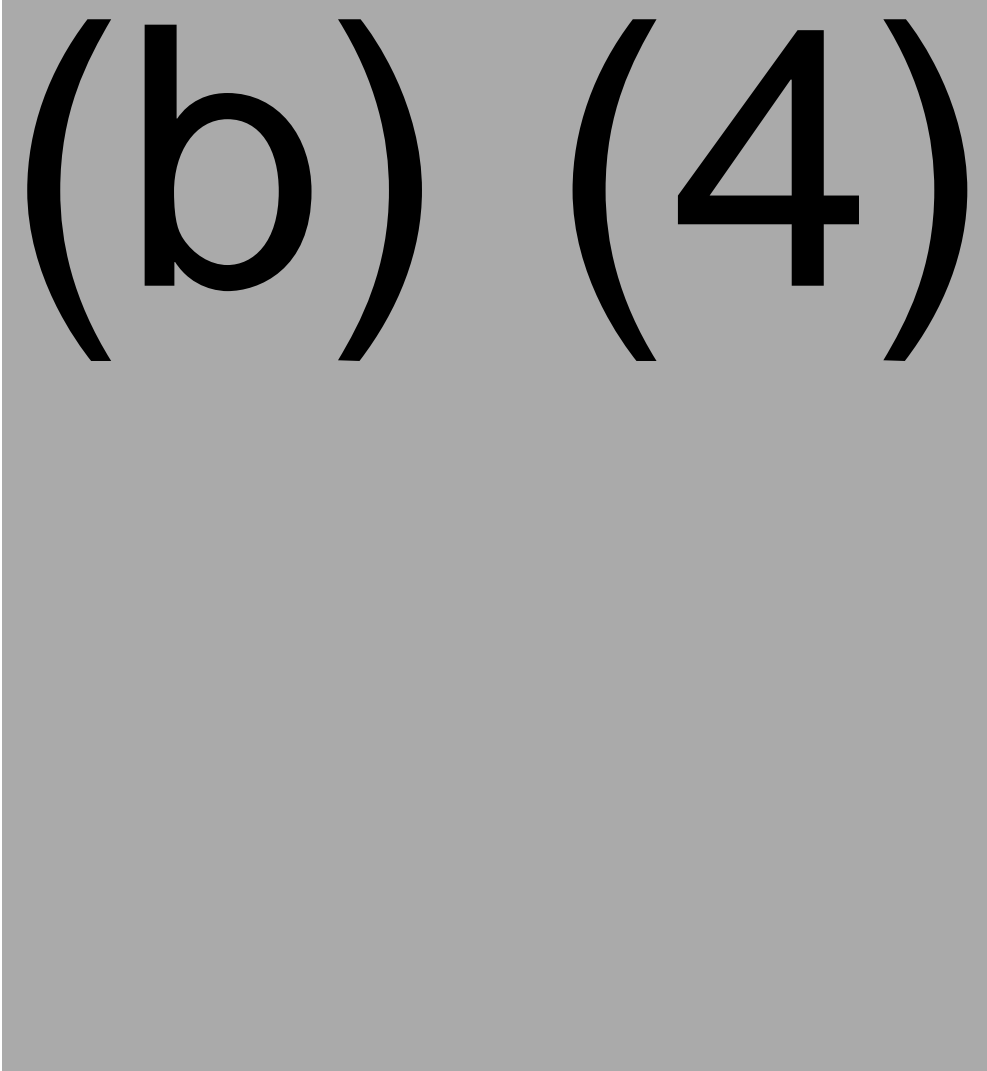
Reviewer Comment: The information provided by MD Anderson in Amendment 125657/0.6 is acceptable: (b) (4) water is used to (b) (4) used to clean the facility.

2. Heating, Ventilation, and Air Conditioning (HVAC)

a. Design

The original design of the HVAC system was tested to determine the operational status and ability to achieve cleanliness standards of Class (b) (4) and Class (b) (4) and was approved January 2013. The facility was subsequently enhanced during 2015 to increase the airflow, additional high efficiency particulate air (HEPA) filters, changes made to return (b) (4), and additional return (b) (4) to the January 2016 as-built specifications. No changes have been made since February 2016.

The HVAC system serving the classified manufacturing/testing laboratory space is designed to provide pre-filtered, temperature conditioned air to (b) (4) electric fan-powered high efficiency particulate air (HEPA) filtration units with a (b) (4) efficiency rating at (b) (4) which supply the filtered air into the manufacturing and testing area (Figure 3.2.A.1-4).



Supply air flow into the clean room (b) (4) is maintained by constant volume (b) (4) balanced to maintain controlled air volumes to each space. (b) (4) separate air handlers (b) (4), each running at (b) (4) capacity, provide the required volume of air to the facility. The HVAC system is designed that if (b) (4) air handler were to fail, (b) (4) unit can compensate and is capable of maintaining the required air flow and air temperature to maintain proper function of the classified environment. The supply air passes through (b) (4)

Information Request #12 & 13

12. Please provide a description of the composition of the supply air, for example; X% fresh/outside air and X% recirculated.

<p>Reviewer Comment: The information provided by MD Anderson in Amendment 125657/0.6 is acceptable: the supply air is 100% fresh/outside air.</p>
--

13. Please clarify the identification of the (b) (4) air handlers that services the manufacturing and testing areas, due to BLA section 3.2.A.1.1 refers to (b) (4) and HVAC Report refers to (b) (4)

Reviewer Comment: The information provided by MD Anderson in Amendment 125657/0.6 is acceptable: (b) (4) is the proper identification.

The air handler units are powered on (b) (4). All air supplied to the facility passes through HEPA filters with an efficiency rating of (b) (4), powered on an uninterrupted power supply, to ensure filtered air is provided in the clean room. The air exchange rate is approximately (b) (4) air changes/hour in the manufacturing suite and (b) (4) air changes/hour in the testing suite.

A separate, completely independent, HVAC system provides conditioned air to all non-classified areas of the Cord Blood Bank including the freezer room, supply storage, corridors, and administrative / office space areas.

Information Request #14

14. Please provide description and identification (e.g., AHU-X, HVAC-A) of the independent HVAC system that provides conditioned air to all non-classified areas of the Cord Blood Bank.

Reviewer Comment: The information provided by MD Anderson in Amendment 125657/0.6 is acceptable: clarified which rooms in the facility are serviced by the (b) (4) units, and air handlers (b) (4) including the non-classified space. (Note: This information was reviewed during the pre-license inspection).

b. Qualification

HVAC Report (dated December 15, 2015) indicates work was performed from August – October 2015 to modify the supply and return duct work to an open (b) (4) air distribution. The system was tested under (b) (4) operational conditions: (b) (4) air handlers operating simultaneously, and each air handling unit operating on its own. Testing of the system included room differential pressures, air exchange rates, air distribution for the fan filter units, air handling unit data, temperature, and humidity.

The ISO classified clean room is certified (b) (4), with the most recent certification being February 2017. The certification was performed in accordance with ISO standard 14644:2015, and verified the face velocity of each HEPA fan filter unit, HEPA filter operation, differential pressure between adjacent rooms, airflow uniformity, room temperature, room humidity, and airborne particle count. The 2017 certification results confirmed the manufacturing and testing suites and adjacent areas met or exceeded the requirements for (b) (4) environments under dynamic conditions. The 2017 certification was performed by a third party.

c. Environmental Quality

MD Anderson provided the following tables that describe the quality of each room and the activities performed in each.

Table 3.2.A.1-1 Cord Blood Bank Room Detail (Non-Classified Space)

Room	Name	Activity/Function	Critical Equipment
(b) (4)	Lobby	Security enabled entrance to facility	(b) (4)
	Reception	Security enabled entrance to Cord Blood Bank	
	Corridor	Personnel traffic	
	Office	Administration	
	High density filing room	File storage	
	Office	Administration	
	Freezer room	Cryopreservation and storage of HPC, Cord Blood product	
	Main office	Office support personnel – File review	
	Office	Administration	
	Filing Room	Storage for completed Cord Blood Unit files	
	Office Support Area	Workroom and supplies	
	Conference room	Meetings	
	Electrical/Networking	IT Hub	
	Loading Dock	Main entry point for all supplies, equipment. Release and Receipt of cord blood units and samples. Release of product shipments.	
	Blood Culture Incubation	Microbial Culture	
	Janitor closet	Storage for clean room facility cleaning materials	
	Freezer alcove	Refrigerated and frozen storage of supplies/reagents	
	Supply Room	Released supply storage	

(Note: Table above was culled from page 6, Appendix 3.2.A.1. of BLA)

Table 3.2.A.1-2 Cord Blood Bank Room Detail (ISO Classified Space)

Room	Name	Activity/Function	Critical Equipment	ISO Classification
(b) (4)	Clean corridor	Corridor to manufacturing and testing labs	(b) (4)	Class (b) (4)
	Gowning Room	Secure access entrance to clean room processing facility. Primary gowning for entrance to ISO classified facility		Class
	Dressing room	Changing room		Class
	Manufacturing lab secondary gowning	Secondary gowning		Class
	Manufacturing lab	Buffy coat enrichment and cryo-preservative addition		Class
	Supply pass through	Released supply storage		Class
	Testing lab secondary gowning	Secondary gowning		Class
	Lab Exit	Laboratory Exit		Class
	Testing lab	Pre- and Post-Processing Product Characterization		Class
	Testing lab	Pre-processing check-in of cord blood units		Class
	Testing lab	Flow cytometric analysis/enumeration of HPC, Cord Blood product		Class
	Testing lab	Colony Forming Unit Assay setup, incubation, and reading/scoring		Class

(Note: Table above was copied from page 7, Appendix 3.2.A.1. of BLA)

d. Monitoring

A cascading pressure differential is maintained between each room of the facility, the adjacent rooms, and the outside. The manufacturing suite (Room (b) (4)) represents the point of (b) (4) pressure with all adjacent rooms at a (b) (4) pressure. The pressure

differential is designed to prevent/limit potential contaminants from entering the manufacturing suite.

The air handler units, fan filter units, exhaust fans, room temperature, humidity, and differential pressure cascade are monitored through the Building Automation Services (BAS) by MD Anderson Cancer Center facilities personnel. The BAS system automatically notifies the facilities staff when a monitored piece of equipment falls out of range.

Room temperature, humidity, and differential pressure are also monitored by the (b) (4) that is calibrated (b) (4) and maintained by the Cord Blood Bank. The (b) (4) application includes a map of the facility monitoring locations, set points, and current status (i.e., off-line, normal status, in alarm).

Information Request #15

15. Your Building Automation System and (b) (4) appear to have redundant monitoring for the room temperature, humidity, and differential pressures. Please explain the co-operation of these two systems. In addition, please explain the sequence of events of these two systems for notification when a monitored parameter is out of range or in alarm status.

Reviewer Comment: The information provided by MD Anderson in Amendment 125657/0.6 is acceptable: the two monitoring systems are completely independent and use separate inputs, i.e., thermostats, humidity monitors, differential pressure meters. The BAS is monitored 24/7 by MD Anderson Building/Facility Services while the (b) (4) is monitored 24/7 by MD Anderson Cord Blood Bank. Each entity has defined practices for responsibilities and documentation. These systems were evaluated during the PLI.

The (b) (4) procedure (SOP S011.020.004) provides instructions on the use and quality control of the MD Anderson Cord Blood Bank continuous monitoring system. The procedure describes the responsibilities for each personnel level assigned (i.e., system administrator, advanced user, general user), daily review of activity log history each business day, review of reports by quality unit, quarterly mock alarm check, and (b) (4) preventive maintenance including calibration of (b) (4). In addition, the procedure provides instructions for alarm conditions, alarm handling, viewing reports, and reporting to management.

The (b) (4) undergoes full operational verification (b) (4), by the vendor (b) (4). The hardware, software, and associated network connectivity is verified and tested against acceptance criteria relative to functionality. Each (b) (4) is tested in the “As Found” condition. Any out of tolerance (b) (4) are calibrated and an assessment of impact is performed.

Reviewed *Operational Verification and Input Calibration of the* (b) (4) (Document MM-VP-00003) executed in June 2016. During the pre-license inspection, I reviewed the (b) (4) calibration of the (b) (4) executed in 2017.

3. Facility Controls

a. Cleaning/sanitization procedures

Cleaning of the CBB ISO classified area is performed on routine basis by trained staff, using cleaning agents per manufacturer's instructions. Cleaning is performed by two different units: CBB personnel and Housekeeping personnel from the Patient Care and Facilities Management (PCFM) department of MD Anderson.

Cleaning performed by CBB personnel

Cleaning agents include (b) (4) disinfectant and (b) (4)

Cleaning activities include:

Frequency	Article
(b) (4)	(b) (4)

Cleaning performed by PCFM personnel

Facility Cleaning SOP S009.003.004 defines the order for performing the cleaning, the cleaning agents, replacement of cleaning supplies during the cleaning process, proper gowning, frequency, and cleaning of classified and non-classified areas. The cleaning agents include (b) (4) disinfectant.

Frequency	Article
(b) (4)	(b) (4)

(b) (4)

b. Personnel gowning practices

The CBB ISO classified areas are designed for personnel to enter and exit by separate ante rooms, and require donning of primary and/or secondary gowning. Primary gowning consists of scrubs, clean room shoes, hair cover, bread cover, lab coat, gloves, and shoe covers. Referring to Figure 1 below, primary gowning is worn in the (b) (4) Clean Access corridor (3), Validated Supply Pass Through room (5), Manufacturing Gowning room (4), QC Gowning room (6), and (b) (4) Accession room (7).

Secondary gowning consists of the primary gowning, and donning a second pair of shoe covers followed by sanitizing gloved hands. The required gowning appears suitable for the activities performed. Assessment of staff training and qualifications will occur during the pre-license inspection. The figure below indicates the (b) (4) classified areas where secondary gowning is worn: Manufacturing Lab (11), QC Lab (10), Test Lab (9), Flow Lab (8), and Accession Room (7).

(b) (4)

c. Security / Access control

The security of the facility is maintained by card access, monitored by a 24-hour camera system, and University to Texas Police Department (UTPD) staff. Video monitoring by UTPD includes the (b) (4)

Entrance into the facility requires a minimum of (b) (4)

d. Environmental Monitoring Program

The CBB has established an environmental monitoring (EM) program (S 009.008.002) to monitor the (b) (4) areas, including (b) (4) classified biological safety cabinets (BSC). The EM program includes non-viable particulates, active and passive viable particulates, settling plates, and surface sampling in the classified areas. In addition, the EM program has established alert and action levels. Quality Assurance reviews and tracks the results of the EM program. Trending of results and outcome of investigations are reported to the CBB Director at regular quality assurance meetings.

The manufacturing and quality control labs are equipped with (b) (4) classified biological safety cabinets; (b) (4) in manufacturing (Room (b) (4) and (b) (4) in quality control (b) (4) in Room (b) (4) and (b) (4) in Room (b) (4), the BSC is monitored for non-viable particulates (b) (4), each BSC is monitored for passive viable particulates (b) (4).

EM Schedule and Locations (I 085.055.002) provided the monitoring frequencies and locations. The (b) (4) monitoring locations includes the manufacturing and testing areas, biological safety cabinets, gowning, pass-throughs, entrances and exit to the (b) (4) area, as well as the main clean facility corridor. The (b) (4) areas within the gowning, testing, and manufacturing areas are monitored (b) (4) for non-viable and viable particulates, under static and dynamic conditions. (b) (4) monitoring includes additional locations within the gowning, testing, and manufacturing (b) (4) areas that are monitored for viable and non-viable particulates (b) (4). In addition, the (b) (4)

Environmental Monitoring Program Acceptance Criteria is as follows:

Table 3.2.A.1-3 Non-Viable Airborne Particle Acceptance Criteria

Sample Location	Acceptable (Particles	Alert (Particles	Action (Particles	Fail (Particles
(b) (4)				

Table 3.2.A.1-4 Viable Airborne Particle Acceptance Criteria

Viable Particle Active Air Sampling

Sample Location	Acceptable (CFU/m ³)	Alert (CFU/m ³)	Action (CFU/m ³)
(b) (4)			

Viable Particle Air Sampling (b) (4)

Sample Location	Acceptable (CFU/90mm plate)	Action (CFU/90mm plate)
ISO 5	≤ 3	> 3

Surface Sampling (b) (4)

Sample Location	Acceptable (CFU/RODAC plate)	Action (CFU/RODAC plate)
(b) (4)		

(Note: Tables 3.2.A.1-3 and 3.2.A.1-4 were culled from page 14, Appendix 3.2.A.1 of the BLA).

Information Request #16

16. Appendix 3.2.A.1, *Facilities and Equipment*, page 14, Tables 3.2.A.1-3 and 3.2.A.1-4 provides your acceptance criteria for non-viable and viable particles, respectively.

Your (b) (4) classified areas are sampled (b) (4) under static and dynamic conditions. Please indicate if the acceptance criteria are applicable for results collected under static or dynamic conditions, or both.

Reviewer Comment: Amendment 125657/0.6 clarified that the above acceptance criteria is applicable for both static and dynamic conditions. The environmental monitoring practices and data were assessed during the PLI.

4. Computer Systems

b. Overview

MD Anderson provided a list of their computer systems. All systems are hosted within MD Anderson's firewall. User level access control is required for each computer system and is administrated by the Cord Blood Bank.

The list included systems that control critical manufacturing processes, as well as support functions. Systems that control critical manufacturing steps are the (b) (4)

(b) (4) In addition, the list included (b) (4) which is a continuous monitoring system of the clean room facility and critical equipment. Refer to Establishment Description section III.B.2.d for more details.

The following table includes the system name, system function, the manufacturing step(s) controlled by the system, and the developer.

System Name	System Function	Manufacturing Step(s) Controlled	Developer
-------------	-----------------	----------------------------------	-----------

(b) (4)

c. Change Management

MD Anderson Cord Blood Bank (CBB) has a defined process for implementing changes to the informatics systems. Review of *CBB Informatics Change Control* (SOP S010.017.001) states that a change request is submitted to the CBB Informatics Group with the approval of the CBB Assistant Director or Manager of Quality Control. The change request is logged and assigned to a CBB Clinical Informatics Team member. A risk-based analysis, including a cross-system impact analysis when applicable, is made to determine if any predicated risk or system impact may result from executing the change. If significant risk or impact is identified, the change request is further evaluated and is approved or disapproved by a CBB Informatics Team member.

All changes are tested and validated prior to implementation. The scope of the validation is based on the scope of the change and associated risk to the cord blood unit and potential recipients. Following satisfactory validation and approval by the technical administrator and quality assurance, the change is implemented, along with industry standard monitoring for any negative impacts. End-users are notified of the change.

d. Cord Blood Information System (CBIS)

The CBIS captures cord blood processing from collection, manufacturing, cryopreservation, and shipping.

- The CBIS generates the unique cord blood identifier (CBID), in collection site specific batches. The CBIDs are used for labeling all consent and collection documentation, samples, and units. The labels are printed using a validated printer that automatically scans and verifies each barcode label as it is printed.
- All maternal demographics, maternal risks, and family history information recorded during the donor screening process is captured electronically
(b) (4) The data is imported into the CBIS using a validated import process
(b) (4)
- All maternal and cord blood testing is captured in CBIS.
 - Infectious disease and ABO/Rh testing are imported electronically into the CBIS from the vendor using a validated import function (Lab Data Import Validation).
 - Hemoglobinopathy and Sterility test results are entered manually. ABO/Rh and infectious disease testing may be entered manually. All manually entered data is performed using (b) (4) entry process to ensure accuracy (CBIS Data Entry Validation).
- Cord blood unit processing is captured in CBIS using an interface that follows the workflow process for each cord blood unit, allowing for concurrent data capture.
 - Labeling used during the manufacturing process is printed on demand, reviewed, scanned, and verified the barcodes as correct and readable.
 - The consumable supplies and equipment used in each step of the manufacturing process are recorded by scanning the assigned, unique product barcode into the CBIS. Data captured during manufacturing is evaluated in real-time to ensure the data is complete and within specification. Unacceptable data requires a review or rejection of the workflow processing task before the processing task is completed and proceed to the subsequent task. All review and rejection activities are captured.
- Shipment data including recipient demographics, HLA, Transplant Center/Processing Lab address, and confirmatory HLA data for capture in CBIS.

Inspection Follow-up: The electronic records created, maintained, stored, retrieved, and transmitted/uploaded using CBIS meets the definition of electronic records per 21CFR Part 11. No data integrity issues were identified during the PLI.

Validation of the CBIS included:

Description	Validation Summary
Printing Collection Lot Label (Printing Lot Labels)	Validation Successful: Labels successfully printed, verified, and dispensed for use.
Manually entry of maternal and infant donor data using CBIS Interface	Validation Successful: Manually completed data (contact information, race, ethnicity, medical questions, labor and

(Donor Data Entry)	delivery were saved correctly and matched the audited data.
Import of data collected electronically using (b) (4) into CBIS (b) (4)	Validation Successful: Data from (b) (4) cord blood units completed using (b) (4) and imported into CBIS. Data viewed in CBIS post-import confirmed data imported matched (b) (4) data. One unexpected finding dealt with a display issue; unrelated to import process. Issue corrected and all data imported displayed properly.
Import of infectious disease testing results and cord ABO/Rh data (Lab Data Import)	Validation Successful: Data for (b) (4) cord blood units for all tests and the associated result were imported correctly using the interface and were stored correctly in the database. Data for (b) (4) cord blood units imported and data confirmed to be store and displayed properly.
Workflow and processing data entry for manufacturing of cord blood units (Processing Data Entry)	Validation Successful: (b) (4) test cases performed to test multiple processing outcomes including both conforming and non-conforming cord blood units. Electronic data entry, on demand label printing and generation, report generation and review were validated. Minor deviation due to test script error.

e. (b) (4)


(b) (4)

(b) (4)

(b) (4)

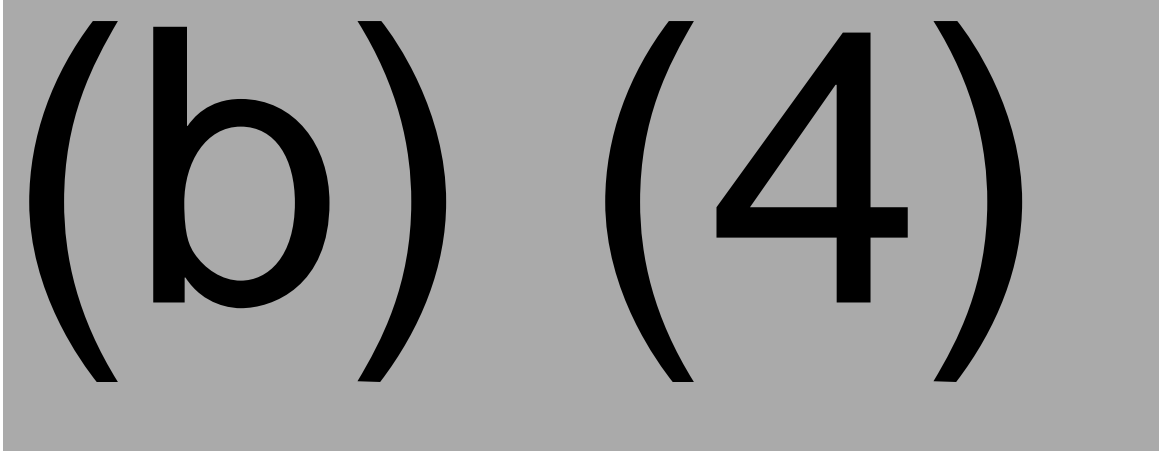
Prior to review for listing, the donor eligibility is made by trained CBB staff using all data obtained from donor evaluation and testing. The outcome of the donor eligibility determination is recorded in (b) (4) and subsequently confirmed by the CBB Director.

(b) (4)




Validation of (b) (4) included:

Description	Validation Summary
(b)	(4)



f. (b) (4)




Validation of (b) (4) included:

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



g. (b) (4)



Validation of (b) (4) included:

Description	Validation Summary
(b) (4)	(b) (4)

Information Request #17

Please address our concerns related to your software and associated validation for manufacture of your product:

- A. Describe the process by which change requests are submitted to the clinical informatics team;
- B. Provide a list of the individual roles and responsibilities who comprise the clinical informatics team;
- C. Provide the process which determinates the level of risk associated for any given change request;
- D. You have not demonstrated that your validation technique for (b) (4) is adequately robust for any given type of change request and associated risk level. Please provide a detailed validation summary that will be used;
- E. Provide the process by which approved changes from the clinical informatics team are coordinated with the software developers;
- F. Provide the software version that was validated for (b) (4)
- G. Provide the method by which the software version number is updated for these software programs based on major and minor changes;
- H. Provide the method by which software updates are performed on these systems and the personnel responsible for the update.

Reviewer Comment: The response to the Information Request was not received until after the PLI. Therefore, the computer systems were further evaluated during the PLI. A 483-observation dealt with processes for updating the computer system due to receiving subsequent identity (i.e., ABO/Rh and HLA) and safety (i.e., infectious disease) testing results. A follow-up teleconference was held post-inspection. Response in Amendments 125657/0.5, 125657/0.6 and 125657/0.7 were found acceptable for both the Information Request and PLI issues.

h. (b) (4)

(b) (4)

G. Contamination / Cross-Contamination

1. Equipment Cleaning Procedures and Validation

Equipment used in the classified area (b) (4) for manufacturing HPC, Cord Blood is cleaned (b) (4). Equipment is cleaned with an approved (b) (4), or both.

MD Anderson states that because the manufacture of HPC, Cord Blood is performed in a closed system, and there is no direct contact between the product and the equipment, validation of removal of cleaning agent residues is not required. I agree with this rationale; however, the instructions for use for each cleaning agent need to be submitted for review.

Inspection Follow-Up: Cleaning agents used to clean the facility and equipment were further evaluated during the PLI, including preparation, usage, and compliance with manufacturer's instructions. No issues identified.

2. Containment Features

The primary mode of contamination control is the use of closed processing systems, comprising of sterile, disposable, single-use materials for the manufacture of the HPC, Cord Blood. The functionality of the closed system is supported by process simulations and product sterility testing. When the manufacturing process requires a sterile connection, the connection is made using a tube welder, and the weld is inspected prior to proceeding to the next manufacturing step.

In addition, the combination of engineering, personnel, environment, and facility controls have been established to minimize contamination / cross-contamination during the receipt, processing, storage, and distribution of the HPC, Cord Blood. Said controls include:

- Engineering - HEPA filtered air in the (b) (4) (manufacturing and testing suites) and (b) (4) (adjacent areas), differential pressure, interlocking pass-through units and doors, biological safety cabinets
- Personnel - gowning, training, disinfecting gloves with (b) (4)
- Environment – monitoring of utilities and environmental conditions (temperature and humidity), ISO classification, temporal and spatial segregation of manufacturing activities, including processing of one unit at a time

- Facility - access, (b) (4) flow of materials/personnel/product/waste, cleaning procedures, handling of biohazardous materials

If there is a breach in container integrity and product leaks on to the equipment, the manufacturing process in the immediate area is suspended. The equipment and surfaces are disinfected in accordance with *SOP CBB 009.011.001, Cord Blood Bank Cleaning Procedure*, which also refers the operator to the equipment owner's manual for additional instructions and guidance. Once the equipment and surfaces have been decontaminated, the manufacturing process may resume.

IV. CONCLUSION

The information request and 483 observation responses have adequately addressed each concern raised during the review of this BLA. Therefore, I am recommending approval of this HPC, Cord Blood BLA.