Summary Basis for Regulatory Action Template

Date: June 21, 2018

From: Mercy Quagraine, Ph.D., Chair of the Review Committee

STN#: 125657/0

Applicant Name: MD Anderson Cord Blood Bank (MDACBB)

Date of Submission: June 26, 2017

Goal Date: June 26, 2018

Proprietary Name: None

Non-Proprietary Name: HPC, Cord Blood

Indication: Hematopoietic Progenitor Cell (HPC), Cord Blood, is an allogeneic cord blood hematopoietic progenitor cell therapy indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment. The benefit-risk assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.

Recommended Action: The Review Committee recommends approval of this product.

Office of Tissues and Advanced Therapies Signatory Authority:

Wilson W. Bryan, M.D., Director, Office of Tissues and Advanced Therapies

- ☐ I concur with the summary review.
- ☐ I concur with the summary review and include a separate review to add further analysis.
- ☐ I do not concur with the summary review and include a separate review.

Office of Compliance and Biologics Quality Signatory Authority:

Mary A. Malarkey, Director, Office of Compliance and Biologics Quality

- ☐ I concur with the summary review.
- ☐ I concur with the summary review and include a separate review to add further analysis.
- ☐ I do not concur with the summary review and include a separate review.

The table below indicates the material reviewed when developing the SBRA

Document title	**Reviewer name, Document date**
CMC Review(s) • *CMC (product office)*	Mercy Quagraine, PhD / June 20, 2018 PrajaktaVaradkar, PhD / June 20, 2018 Heba Degheidy, MD, PhD / June 20, 2018 Hanh Khuu, MD / June 20, 2018 Shyh-Ching Lo, MD, PhD / June 20, 2018 Donald Fink, PhD / June 20, 2018 Steven Oh, PhD / June 20, 2018 Raj Puri, MD, PhD / June 20, 2018
• *Facilities review (OCBQ/DMPQ)*	Joyce Rockwell / June 4, 2018 Bradley Dworak, PhD / May 8, 2018 Carolyn Renshaw / June 4, 2018 Jay Eltermann / June 4, 2018
• *Establishment Inspection Report (OCBQ/DMPQ)*	Joyce Rockwell / May 8, 2018 Bradley Dworak, PhD / May 8, 2018 Mercy Quagraine, PhD / May 8, 2018 Heba Degheidy, PhD / May 8, 2018 Prabhu Raju / May 8, 2018
Clinical Review(s) • *Clinical (product office)*	Meghna Alimchandani, MD / May 18, 2018 Lei Xu, MD / May 18, 2018 Tejashri Purohit-Sheth, MD / May 18, 2018
Statistical Review(s) • *Clinical data*	Yuqun (Abigail) Luo, PhD/ May 18, 2018 Shiowjen Lee, PhD/ May 18, 2018
Pharmacology/Toxicology Review(s) • *Toxicology (product office)*	Jinhua Lu, PhD / February 26, 2018 Mercedes Serabian, MS, DABT / February 26, 2018
Labeling Review(s) • *APLB (OCBQ/APLB)*	Michael Brony / May 30, 2018 Lisa Stockbridge / June 1, 2018
Advisory Committee summary	NA

1. INTRODUCTION

MD Anderson Cord Blood Bank (MDACBB) submitted a Biologics License Application (BLA) 125657 to seek licensure of HPC (Hematopoietic Progenitor Cell), Cord Blood. HPC, Cord Blood is an allogeneic hematopoietic progenitor cell therapy indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment. The benefit-risk assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.

This document summarizes the basis for the approval of HPC, Cord Blood. All findings identified during the review of the BLA have been adequately addressed. The review team recommends marketing approval of the product.

2. BACKGROUND

HPC, Cord Blood is rich in hematopoietic progenitor cells, and has been used in the treatment of a variety of disorders, including hematologic malignancies, metabolic disorders, and immunodeficiencies.

Regulatory History

In an October 2009 Federal Register notice, FDA announced that manufacturers of cord blood will be required to have an approved BLA or IND in effect for unrelated cord blood shipped after October 20, 2011.

FDA developed and finalized guidance for industry entitled *Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications (October 2009).* Updates from FDA's re-examination of the legacy docket data and FDA's consideration of the proceedings of the September 2011 Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) meeting were included in the new, updated final *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,* issued in March 2014. This guidance provides recommendations for the submission of a BLA for placental/umbilical cord blood.

On June 26, 2017, MDACBB submitted a BLA to request licensure of its HPC, Cord Blood. The applicant followed FDA guidance recommendations and cited Dockets FDA-1997-N-0010 (Legacy Docket number 97N-0497), and FDA-2006-D-0157 (Legacy Docket number 06D-0514) for the efficacy and safety data to support this application.

The BLA includes the applicant's safety outcomes dataset to support the safety of the product.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

a) Product Quality

Product Description

HPC, Cord Blood, the subject of this BLA, is manufactured by MDACBB. The proprietary name, '*MD Anderson Cord*' was reviewed and found unacceptable by the Agency. The applicant declined to propose another name for review and hence, has decided to use the proper name, HPC, Cord Blood. The manufacture of HPC, Cord Blood at MDACBB is consistent with recommendations made in the FDA guidance on BLA for cord blood licensure referenced above.

Mothers who consent to donate their newborn's cord blood for public banking are screened and tested for communicable infectious diseases per regulations in 21 CFR 1271 Subpart C. Cord blood is collected from mothers who screen and test negative for the relevant communicable disease agents or diseases. The applicant has arrangements with five local and two out-of-state hospitals to collect cord blood. The collected cord blood units are transported to the processing facility by couriers (dedicated couriers for local hospitals, commercial carriers for out-of-state hospitals) using validated and temperature-monitored shipping containers.

The cord blood is processed by volume reduction and partial red blood cell and plasma depletion using the (b) (4) system (a class II medical device cleared by FDA for cord blood processing). The final volume of HPC, Cord Blood is 25 ml and contains 10% DMSO and 1% Dextran 40. Each lot is frozen using a controlled-rate freezing process and then stored in the liquid phase of liquid nitrogen (≤-150°C). The HPC, Cord Blood final product is tested for safety, purity, identity, and potency.

HPC, Cord Blood is cryopreserved in a two-compartment freezing bag. The larger compartment contains 80% of the cell suspension (20 ml) and the smaller contains 20% (5 ml). The cryobag is placed in a (b) (4) 'overwrap' bag and maintained inside a protective metal canister for freezing and storage in liquid nitrogen in the (b) (4)

HPC, Cord Blood will have a (b) (4) dating period per data provided in the BLA to date. There is a stability program in place to potentially (b) (4)

HPC, Cord Blood is shipped frozen in special shipping containers (Dry-Shippers) designed to maintain a controlled environment and a very low temperature (≤-150°C). Shipping and receiving of HPC, Cord Blood in the dry-shipper must occur within (b) (4) and temperature is electronically monitored and recorded for the entire transit time.

The thawing and preparation procedures have been validated. Directions for thawing are appended to the end of the prescribing information in the section "Instructions for Preparation for Infusion", and will be included with each shipped lot of HPC, Cord Blood.

Manufacturing Controls

Process and product controls are in place to assure the quality of HPC, Cord Blood. There are specified time limits for all manufacturing steps; cord blood is processed and frozen within (b) (4) of collection. Lot release is based on a combination of in-process testing results as well as final product testing. A total nucleated cell (TNC) count on the collected cord blood is performed upon receipt at the MDACBB processing facility, and a cord blood unit is processed only if it contains (b) (4) cells. A summary of the lot release tests performed on each lot of HPC, Cord Blood is shown in Table 1. Infectious disease testing is performed on a maternal blood sample; hemoglobin analysis and ABO/Rh typing are performed on pre-processing cord blood samples; and the rest of the testing is performed on post-processing cord blood samples. All lot release tests must meet specifications for the product to be released into search inventory. Confirmatory HLA typing is performed on the HPC, Cord Blood sample in a cryobag segment at the time of release for transplantation.

Table 1. MD Anderson Lot Release Acceptance Criteria for HPC, Cord Blood

Product Characteristics	Testing	Sample Type and Timing)	Specification
Safety	**Infectious Diseases Testing Required (21 CFR 1271.45 through 1271.90)** HBSAg Anti-Hep B core Anti-HCV Anti-HIV-1/2 Anti-HTLV-1/2 Anti-Trypanosoma cruzi (Chagas) HIV RNA/HCV RNA/HBV DNA West Nile Virus RNA Syphilis Cytomegalovirus (CMV)	Maternal blood sample obtained with 7 days of cord blood collection. 21 CFR 1271.80 (a) (b)	All tests negative, except CMV CMV results-Report
	Sterility	(b) (4)	No growth at (b) (4)
	Hemoglobinopathy	(b) (4)	(b) (4)
Purity and Potency	Total CD34+ cell count	HPC, Cord Blood (pre-cryopreservation)	≥1.25 x 10^6/HPC, Cord Blood
	Total Nucleated Cell (TNC) count (per HPC, Cord Blood)	HPC, Cord Blood (pre-cryopreservation)	(b) (4)
	Nucleated RBC	HPC, Cord Blood (pre-cryopreservation)	(b) (4)
	Viability Nucleated cell (b) (4)	HPC, Cord Blood (pre-cryopreservation)	(b) (4)
	Viability- CD34+ cells (b) (4)	HPC, Cord Blood (pre-cryopreservation)	(b) (4)
	Colony Forming Units (CFU) assay	HPC, Cord Blood (pre-cryopreservation)	Growth
Identity	Initial Human Leukocyte Antigen (HLA)	HPC, Cord Blood (pre-cryopreservation)	Report
	Confirmatory HLA	Attached segment	Report
	ABO/Rh Type	Cord blood	Report
Volume	Cord Blood Volume at collection	Cord Blood	(b) (4)

Manufacturing Risks

The greatest risks associated with the manufacture of HPC, Cord Blood are 1) the risk of transmitting communicable diseases, 2) the risk of product contamination, particularly during collection of the cord blood and also during processing, and 3) the potential for decrease in product potency during thawing/washing. These risks are mitigated/minimized by various approaches.

To address the communicable disease risks, medical records are reviewed for high-risk exclusion, and mothers of the newborn donors are also screened and tested for communicable diseases according to the 21 CFR 1271 regulations. Cord blood collection is performed in designated areas or delivery suites by staff or healthcare providers trained to use aseptic technique, and to collect one cord blood unit at a time.

Each collected cord blood unit is given a unique bar code ID number (ISBT) which is both visually and mechanically readable. This bar code is associated with all test results for maternal and cord blood, and with the matched patient.

To address contamination risks, collection and processing methods are functionally closed and have been validated to ensure aseptic processing. The cryoprotectant is added to the processed HPC, Cord Blood using aseptic technique. Post-processing samples are tested for microbial contamination and must be negative.

To preserve cell potency, HPC, Cord Blood is frozen using a controlled-rate freezing process and stored in a liquid nitrogen freezer (≤-150°C). The HPC, Cord Blood is placed in a (b) (4) 'overwrap' bag before being placed in the metal canister for freezing.

The applicant has provided data to validate the freezing and thawing/washing procedures and to establish the product dating period. Based on the stability data submitted to the BLA, the current dating period for HPC, Cord Blood is (b) (4) The applicant has a stability program in place to (b) (4) , if appropriate.

b) CBER Lot Release

An exemption has been granted from CBER Lot Release testing, including no requirement for submission of product samples to CBER. The basis for this decision is the fact that each lot is a single HPC, Cord Blood unit that will treat a single patient. CBER Lot Release testing would negatively impact the limited quantity of cells available to the patient, and failure of a single lot will have minimal impact on public health.

c) Facilities review/inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of HPC, Cord

Blood is listed in the table below. The activities performed and inspectional history are noted in the table and further described in the paragraph that follow.

Manufacturing Facilities Table for HPC, Cord Blood

Name/address	FEI number	DUNS number	Inspection/ waiver	Results/ Justification
HPC, Cord Blood Manufacturing, Labeling, and Testing MD Anderson Cord Blood Bank 1841 Old Spanish Trail Houston, TX 77054	3010547404	800772139	Pre-license Inspection	CBER Feb 26 – March 2, 2018 Voluntary Action Indicated (VAI)

CBER conducted a pre-license inspection (PLI) of MD Anderson Cord Blood Bank from February 26 - March 2, 2018. At the end of the inspection, a Form FDA 483 was issued. The firm responded to the observations, and the corrective actions were reviewed and found to be adequate. All inspectional issues have been satisfactorily resolved.

Container Closure System

The cord blood is processed using the (b) (4) Processing System [cleared class II device (b) (4) and a (b) (4) Disposable Kit, which is a closed system. The final product is filled into a sterile, dual fractionated (80% / 20%), Biosafe (b) (4) cryobag [cleared class II device (b) (4) The validity of the filling process and integrity of the final product bags were demonstrated through the execution of aseptic process simulations and acceptable sterility testing.

d) Environmental Assessment

The BLA includes a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

No pharmacology/toxicology studies were conducted with HPC, Cord Blood manufactured by MD Anderson Cord Blood Bank, due to the minimal manipulation of the product and the previous human experience with HPC, Cord Blood from multiple cord blood banks.

5. CLINICAL PHARMACOLOGY

No studies of drug interactions have been performed with applicant's HPC, Cord Blood.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

This BLA proposes the use of the applicant's HPC, Cord Blood in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment. The BLA submission includes data from clinical experience with the MDACBB product, and references data in the Dockets FDA-1997-N-0010 (Legacy Docket number 97N-0497) and FDA-2006-D-0157 (Legacy Docket number 06D-0514). The review team also considered the available scientific literature and the results of the Cord Blood Transplantation (COBLT[1]) study. The review team determined that the BLA submission was sufficient for assessment of the safety and effectiveness of HPC, Cord Blood manufactured by MDACBB.

Clinical Efficacy Review

The effectiveness of HPC, Cord Blood for achieving hematopoietic reconstitution has previously been established by FDA analyses of the pooled HPC, Cord Blood dataset of the docket, as well as the COBLT study and other published observational studies. Assessment of hematopoietic reconstitution was based primarily on analyses of neutrophil and platelet recovery of patients who received a suitable allograft (i.e., a total nucleated cell dose (TNC) $\geq 2.5 \times 10^7$/kg and $\geq$ 4/6 degree of human leukocyte antigen (HLA) match). Among the 846 patients, the cumulative incidence of neutrophil recovery defined as absolute neutrophil count (ANC) greater than 500 cells/μL by Day 42 was 88.2%, similar to that demonstrated in the pooled docket dataset (77%) and in the COBLT study (76%). The median time from transplantation to an ANC greater than 500 cells/μL was 19 days, also comparable to the docket dataset (25 days) and COBLT study (27 days). The cumulative incidence of platelet recovery, defined as a platelet count greater than 20,000 cells/μL by Day 100, was 73.6%, and the median time from transplantation to a platelet count greater than 20,000 cells/μL was 47 days. Analysis of docket data has indicated that the TNC dose and degree of HLA match are inversely associated with the time to neutrophil recovery. Sixty-six percent (N = 862) of the 1,299 patients in the docket dataset who received a TNC dose $\geq 2.5 \times 10^7$/kg underwent transplantation as treatment for hematologic malignancy. Results for patients who received a suitable allograft with the MDACBB product are compared to the

[1] Cornetta K, Laughlin M, Carter S, et al. Umbilical cord blood transplantation in adults: results of the prospective Cord Blood Transplantation (COBLT). Biol Blood Marrow Transplant 2005;11:149-60.

hematopoietic reconstitution data from the docket dataset and the COBLT study in Table 1.

The efficacy of the HPC, Cord Blood product is assessed in terms of hematopoietic reconstitution in patients who received a suitable cord blood allograft (TNC ≥ 2.5 x 10^7/kg of recipient weight, and ≥ 4/6 degree of HLA match with patient). The MDACBB dataset included 846 patients who received a suitable allograft with 100-day follow-up data. The clinical data, as illustrated in Table 1, provide evidence that transplantation with the applicant's HPC, Cord Blood results in hematopoietic reconstitution as demonstrated by neutrophil and platelet recovery. The primary graft failure rate for patients receiving a TNC dose ≥2.5 x 10^7/ kg was 16% in the pooled docket dataset, and 12% in patients who received a suitable allograft with the applicant's HPC, Cord Blood. The MDACBB dataset does not include information regarding immunologic reconstitution. However, based on the analyses of the docket data and supported by the publicly available data, HPC, Cord Blood has demonstrated the ability for immunologic reconstitution for patients transplanted for primary immunodeficiency as well as for other malignant and nonmalignant disorders. Considering these data, the review team concludes that this BLA provides substantial evidence that the MDACBB HPC, Cord Blood is effective for the proposed indication.

Table 1: Summary of Efficacy Demonstrated by Hematopoietic Reconstitution

[Source: Table 2.6-1 *Summary of Clinical Studies*, response to statistics information request dated March 27, 2018]

Data Source	**The COBLT Study**	**Docket and Public Data**	**MDACBB***
Design	Single-arm prospective	Retrospective	Retrospective
Number of patients	324	1299	846
Median age (range) in years	4.6 (0.07 - 52.2)	7.0 (<1 – 65.7)	24.8 (0.1 – 73.3)
Sex	59% Male 41% Female	57% Male 43% Female	58% Male 42% Female
Median weight at transplant (kg) (range)	NA	NA	59.0 (2.6 – 146)
Median TNC Dose (x 10^7/kg) (range)	6.7 (2.6 – 38.8)	6.4 (2.5 – 73.8)	5.4 (2.5 – 76.9)
Neutrophil Recovery at Day 42 (ANC > 500/μL) (95% CI)	76% (71%, 81%)	77% (75%, 79%)	88.2% (85.9%, 90.2%)
Platelet Recovery at Day 100 (20,000/μL) (95% CI)	57% (51%, 63%)	NA	73.6% (70%, 77%)
Platelet Recovery at Day 100 (50,000/μL) (95% CI)	46% (39%, 51%)	45% (42%, 48%)	43% (39%, 46%)
Erythrocyte Recovery at Day 100 (95% CI)	65% (58%, 71%)	NA	NA
Median time to Neutrophil Recovery	27 days	25 days	19 days
Median time to Platelet Recovery (20,000/μL)	90 days	NA	47 days
Median time to Platelet Recovery (50,000/μL)	113 days	122 days	65 days
Median time to Erythrocyte Recovery	64 days	NA	NA

Data from patients who received a suitable allograft (TNC ≥ 2.5 x 10^7/kg and ≥ 4/6 HLA match). Note that evaluable data for outcomes were not available for all patients and there are various amounts of missing data.
NA: data not available

Assessment of efficacy in the BLA review is based on voluntary data collection, and evaluable data for outcomes were not available for all patients in the MDACBB dataset. While the data suggest favorable trends in favor of the applicant's HPC, Cord Blood, the data are insufficient to support its superior effectiveness due to limitations of the retrospective dataset. Comparisons of the applicant's dataset to the COBLT and docket

datasets are limited by the following factors: incomplete and missing data from retrospective observational data (including insufficient information about the nature and severity of the diseases that were the primary indications for transplantation and the conditioning regimens) and demographic differences between the applicant's dataset and the docket and COBLT study.

b) Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. The active ingredient, indication, dosage form, dosing regimen, and route of administration of the applicant's HPC, Cord Blood, are not new because they are the same as for the first FDA-approved HPC, Cord Blood, HEMACORD, manufactured by New York Blood Center. Therefore, this application does not trigger PREA.

c) Other Special Populations

The applicant's HPC, Cord Blood has been used in pediatric patients with disorders affecting the hematopoietic system that are inherited, acquired, or resulted from myeloablative treatment. The applicant's HPC, Cord Blood has been used in immunocompromised patients due to either the preparative regimen prior to transplantation or the underlying disease(s). Clinical experience with the applicant's HPC, Cord Blood did not include sufficient numbers of patients ≥ 65 years to determine whether they respond differently than younger patients. There are no data with the applicant's HPC, Cord Blood use in pregnant women to inform a product-associated risk. There is no information regarding the presence of the applicant's HPC, Cord Blood in human milk, the effects on the breastfed infant, or the effects on milk production.

7. SAFETY

The safety analysis of HPC, Cord Blood is based primarily on the docket data, supplemented by the MDACBB data, and taking into consideration the publicly available data. The safety review focused on adverse events (AEs) related to infusion reactions, deaths (Day 100 mortality), graft-versus-host disease, engraftment syndrome, donor cell leukemia, transmission of infection, and transmission of inheritable genetic disorders.

a) Infusion Reactions

Infusion reactions are defined as AEs occurring within 24 hours after transplantation. The causes of infusion reactions may include reactions to hemolyzed HPC, Cord Blood, allergic or anaphylactic reactions to any component of HPC, Cord Blood, or bacterial contamination.

The data from the COBLT study, shown in Table 2, includes exposure to 442 infusions of HPC, Cord Blood (from multiple cord blood banks) in patients treated with TNC >2.5 x 10^7/kg in a single-arm trial. The population, which was 60% male and had a median age of 5 years (range 0.05-68 years), included patients treated for hematologic malignancies, inherited metabolic disorders, primary immunodeficiencies, and bone marrow failure. Preparative regimens and graft-versus-host disease prophylaxis were not standardized. The most common infusion reactions were hypertension, vomiting, nausea, and bradycardia. Hypertension and Grade 3-4 infusion-related reactions occurred more frequently in patients receiving volumes greater than 150 milliliters and in pediatric patients. The rate of serious adverse cardiopulmonary reactions was 0.8%.

Table 2: Incidence of Infusion-Related Adverse Reactions Occurring in ≥ 1% of Infusions in the COBLT Study

Adverse Reaction	Any Grade	Grade 3-4
Any reaction	65.4%	27.6%
Hypertension	48.0%	21.3%
Vomiting	14.5%	0.2%
Nausea	12.7%	5.7%
Sinus bradycardia	10.4%	0
Fever	5.2%	0.2%
Sinus tachycardia	4.5%	0.2%
Allergy	3.4%	0.2%
Hypotension	2.5%	0
Hemoglobinuria	2.1%	0
Hypoxia	2.0%	2.0%

Information on infusion reactions was available from voluntary reports for 846 patients who received suitable allografts with the applicant's HPC, Cord Blood. Table 2 shows that the incidence of infusion reactions with the applicant's product is comparable to the COBLT data. Preparative regimens and GVHD prophylaxis were not standardized. The reactions were not graded for severity. The most common infusion reactions with the applicant's product were hypertension (17.1%), nausea (4.3%), vomiting (3.9%), and headache (1.2%).

Table 2: Incidence of Infusion Reactions
[Source: Table 7 from applicant response to information request dated January 24, 2018]

Infusion Reactions	**Patients who Received ≥ 1 MDACBB Unit with a TNC Dose ≥ 2.5 x 10^7/kg and HLA ≥ 4/6** N = 846	**COBLT Infusions with a TNC Dose ≥ 2.5 x 10^7/kg** Number of Infusions Assessed: N = 442
Total	187 (22%)	65.4%
Hypertension	145 (17.1%)	48.0%
Nausea	37 (4.3%)	12.7%
Vomiting	33 (3.9%)	14.5%
Hypotension	4 (0.5%)	2.5%
Hypoxia	6 (0.7%)	2%
Headache	10 (1.2%)	0
Tachycardia	8 (0.9%)	4.5%
Shortness of breath	7 (0.8%)	0.9%
Chest Pain	7 (0.8%)	0
Fever	6 (0.7%)	5.2%
Chills	2 (0.2%)	0.9
Hives	3 (0.3%)	0
Bradycardia	0	10.4%
Other	26 (3.1%)	

b) Other Adverse Reactions

For other adverse reactions (i.e., other than infusion reactions), the raw clinical data from the dockets were pooled for 1,299 patients (120 adult and 1,179 pediatric) transplanted with HPC, Cord Blood (from multiple cord blood banks) with TNC >2.5 x 10^7/kg. Sixty-six percent (n=862) underwent transplantation as treatment for hematologic malignancy. The preparative regimens and graft-versus-host disease prophylaxis varied. The median TNC was 6.4 (range, 2.5 - 73.8) x 10^7/kg. Limited data on other adverse reactions were also available for patients treated with the applicant's HPC, Cord Blood.

i. Deaths (Day 100 Mortality)

For the 1,299 patients in the pooled docket dataset, Day 100 mortality from all causes was 25%. For the 846 pateints who received a suitable allograft with the applicant's HPC, Cord Blood, Day 100 mortality from all causes was 17%, and the most common causes of death were infection (23%), organ failure (18%) and primary disease (16%).

ii. Primary Graft Failure

Primary graft failure occurred in 12% of patients in the MDACBB dataset. This is comparable to the 16% incidence of primary graft failure in the docket data.

iii. Graft-versus-Host Disease (GVHD)

For patients in the pooled docket dataset who received a TNC dose >2.5 x 10^7/kg, the incidence of acute GVHD was 69%: grades 2-4 GVHD was 42%, and grades 3-4 GVHD was 19%. Data for acute GVHD in the MDACBB dataset was available for 838 patients who received a suitable allograft. Of these patients, 491 (58%) experienced acute GVHD. Chronic GVHD was reported in 136 (16.1%) patients in the MDACBB dataset.

iv. Engraftment Syndrome (ES)

ES occurred in 15% (11.7-18.0%) of the 364 patients in the COBLT study. Median time to onset of the event was 10 days after transplantation (range, 5-35 days). In literature reports, the incidence of ES varies from 30% to 78%. The data in the docket dataset do not address the risk of ES. The MDACBB dataset does not provide any reports of ES associated with the applicant's product.

v. Donor Cell Leukemia, Transmission of Serious Infection, and Transmission of Rare Genetic Disorders

Data from published literature and from observational registries, institutional databases, and cord blood bank reviews reported to the dockets revealed nine cases of donor cell leukemia, one case of transmission of infection, and one report of transplantation from a donor with an inheritable genetic disorder. These data are not sufficient to support reliable estimates of the incidences of these events. The BLA did not provide any reports of donor cell leukemia, transmission of serious infection, or transmission of rare genetic disorders associated with the applicant's HPC, Cord Blood.

Due to differences in the size and quality of the datasets, the review team assessed the safety data from the pooled docket dataset and other publicly available data as the best indicator of the likely postmarketing performance of HPC, Cord Blood. Therefore, the package insert gives precedence to this pooled, publicly available safety data over the MDACBB safety data.

There are no safety issues related to the applicant's HPC, Cord Blood that warrant either a postmarketing requirement (PMR) or postmarketing commitment (PMC) study or a Risk Evaluation and Mitigation Strategy (REMS). The sponsor will conduct routine pharmacovigilance in accordance with 21 CFR 600.80. However, to monitor the postmarketing safety of the product, the review team recommends a postmarketing safety outcomes monitoring and analysis plan, and expedited reporting of serious infusion reactions [see 11(c)].

8. ADVISORY COMMITTEE MEETING

This application was not referred to an Advisory Committee because the product is not the first-in-class and the review team did not identify novel concerns.

9. OTHER RELEVANT REGULATORY ISSUES

Considering the extensive prior clinical experience with HPC, Cord Blood (from multiple cord blood banks), the review team determined that routine pharmacovigilance was adequate for postmarketing surveillance. In addition, review of the BLA did not identify any safety concerns that were not already known for this product class. Postmarket monitoring for the HPC, Cord Blood product class also includes the implementation of a safety outcomes monitoring and analysis plan, and expedited reporting of serious infusion reactions [see 11(c)].

10. LABELING

The Advertising and Promotional Labeling Branch (APLB) found the prescribing information (PI) and carton/container labels to be acceptable from a promotional and comprehension perspective. No proprietary name was submitted.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The review team recommends approval of the applicant's HPC, Cord Blood as indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment. The benefit risk assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.

The recommended minimum dose is 2.5×10^7 nucleated cells/kg at cryopreservation.

b) Risk/ Benefit Assessment

The benefit of the applicant's HPC, Cord Blood is based on hematopoietic and immunologic reconstitution in patients with disorders of the hematopoietic system. Considering the substantial risks associated with HPC, Cord Blood, the benefit-risk assessment is highly individualized. The benefit-risk assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and

specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.

The quality, efficacy, and safety of this product have been thoroughly reviewed and have been determined to be acceptable for use of this product as indicated in the label.

The applicant's HPC, Cord Blood is expected to have a favorable benefit-risk profile.

c) Recommendation for Postmarketing Activities

There are no safety issues related to the applicant's HPC, Cord Blood that warrant either a postmarketing requirement (PMR) or postmarketing commitment (PMC) study or a Risk Evaluation and Mitigation Strategy (REMS). The sponsor will conduct routine pharmacovigilance in accordance with 21 CFR 600.80. The review team recommended, and the applicant agreed to do, the following:

i. Implement a safety outcomes monitoring and analysis plan. This plan will include:

   1) Maintenance of an observational database to include, for all MDACBB HPC, Cord Blood units released, information including but not limited to, time to neutrophil recovery, graft failure, survival, cause of death, infusion reactions, and other adverse experiences;

   2) Aggregate analyses of interval and cumulative adverse experience reports; and

   3) Safety outcomes analyses of interval and cumulative data that address early mortality, graft failure-related mortality, graft failure, time to neutrophil recovery, infusion-related events, and other adverse experiences. Reports will include a description of the population analyzed, results of the analyses, whether outcomes indicators were triggered and, if so, what actions were implemented as a result.

ii. Submit a 15-day alert report for each serious infusion reaction associated with administration of the applicant's HPC, Cord Blood.