Application Type	Original Application
STN	125585/0
CBER Received Date	January 28, 2015
PDUFA Goal Date	January 28, 2016
Division / Office	GMB/DCEPT /OCTGT (Clinical) TEB/DB/OBE (Statistical)
Priority Review	No
Reviewer Name(s)	Clinical: Agnes Lim, M.D. Statistical: Yuqun Abigail Luo, Ph.D.
Review Completion Date / Stamped Date	January 26, 2016
Supervisory Concurrence	Ilan Irony, MD (Branch Chief, OCTGT) Wilson Bryan, MD (Division Director, OCTGT) Shiowjen Lee, PhD (Team Leader, OBE) Boguang Zhen, PhD (Branch Chief, OBE)
Applicant	Puget Sound Blood Center and Program (PSBC)
Established Name	HPC, Cord Blood
(Proposed) Trade Name	<No Proprietary Name>
Pharmacologic Class	Allogeneic Cord Blood
Formulation(s), including Adjuvants, etc.	Each Unit of PSBC HPC, Cord Blood contains: • Active ingredient: a minimum of 5.0×10^8 total nucleated cells (TNC) with a minimum of 1.25×10^6 viable CD34 cells • Inactive ingredients: dimethyl sulfoxide (DMSO), citrate phosphate dextrose (CPD), hydroxyethyl starch, and Dextran 40
Dosage Form(s) and Route(s) of Administration	A cell suspension for intravenous use only
Dosing Regimen	Recommended minimum dose is 2.5×10^7 TNC/kg at cryopreservation
Indication(s) and Intended Population(s)	Puget Sound Blood Center 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 risk-benefit 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.
Orphan Designated (Yes/No)	No

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GLOSSARY

Table 1. Abbreviation and Glossary

AE	Adverse Event
ANC	Absolute Neutrophil Count
BLA	Biologics license application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CD34	A cluster of differentiation molecule present on certain cells within the human body
CI	Confidence interval (95%, unless otherwise specified)
CIBMTR	Center for International Blood and Marrow Transplant Research
CMC	Chemistry, manufacturing, and controls
COBLT	The Cord Blood Transplantation Study
Docket Data	Raw data submitted from multiple cord blood banks and cord blood organizations, such as NMDP, NYBC, and Duke University, to Dockets FDA-1997-N-0010 (Legacy docket number 97N-0497), FDA-2006-D-0157 (Legacy Docket number 06D-0514), and FDA-2009-D-0490
DMSO	Dimethyl sulfoxide
GCP	Good Clinical Practices
GVHD	Graft versus host disease
HLA	Human leukocyte antigen
HPC-A	Hematopoietic progenitor cells, Apheresis
HPC-M	Hematopoietic progenitor cells, Marrow
HSCT	Hematopoietic stem cell transplantation
IND	Investigational New Drug application
NHLBI	National Heart, Lung and Blood Institute
NMDP	National Marrow Donor Program
NYBC	New York Blood Center
PDUFA	Prescription Drug User Fee Act
PeRC	Pediatric Review Committee (CDER & CBER)
PI	Prescribing Information; Package Insert
PLT	Platelet
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PREA	Pediatric Research Equity Act
PSBC	Puget Sound Blood Center Program Cord Blood Services
REMS	Risk Evaluation and Mitigation Strategy
RMS/BLA	regulatory management system for the biologics license application
SAE	Serious adverse event
SCTOD	Stem Cell Therapeutic Outcomes Database
SOP	Standard Operating Procedure
Suitable Allograft	TNC dose at $\geq 2.5 \times 10^7$/kg and HLA match at $\geq 4/6$
TNC	Total nucleated cells

1. Executive Summary

Puget Sound Blood Center and Program Cord Blood Services (PSBC) applied for biologics licensure of Puget Sound Blood Center HPC, Cord Blood, a cord blood product manufactured by the applicant. PSBC HPC, Cord Blood is comprised of hematopoietic progenitor cells (HPC) that are collected from the cord blood donor. The proposed indication is 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 risk-benefit 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 applicant did not conduct any clinical trials to study the efficacy or the safety of PSBC HPC, Cord Blood. To support the safety and efficacy of PSBC HPC, Cord Blood, the applicant submitted their own dataset (PSBC HPC, Cord Blood data) of 537 patients who received allogeneic cord blood units manufactured by Puget Sound Blood Center and Program Cord Blood Services. Of the 537 patients, 290 had sufficient data submitted to determine adequacy of the TNC dose administered; all of these 290 patients received an HLA-matched unit at 4/6 or more. Of these 290 patients, 212 received a suitable allograft, defined as $\geq 2.5 \times 10^7$cells/kg. Additionally, referenced data in the dockets (FDA-1997-N0010 and FDA-2006-D-0157), as well as published literature related to HPC, Cord Blood were used to conduct this review.

The efficacy of HPC, Cord Blood including PSBC HPC, Cord Blood for hematopoietic reconstitution has been established by FDA analyses of the Docket data as well as the COBLT study and other published observational studies. A minimum effective cell dose of $\geq 2.5 \times 10^7$ cells/kg with degree of human leukocyte antigen (HLA) match 4/6 loci and above is defined as a suitable allograft for the purposes of this BLA review.

The efficacy of PSBC HPC, Cord Blood, is defined by hematopoietic reconstitution of patients who received a suitable cord blood allograft. Transplantation of PSBC HPC, Cord Blood, resulted in hematopoietic reconstitution, indicated by neutrophil and platelet recovery. Neutrophil recovery is defined as the time from transplantation to an absolute neutrophil cell (ANC) count more than 500 per microliter (ANC >500/µL). Platelet recovery is the time from transplantation to a platelet count more than 20,000 per microliter (>20,000/µL). The docket data demonstrate that the TNC dose and degree of HLA match are inversely associated with the time to neutrophil recovery. Table 2 summarizes the efficacy data. The cumulative incidence of neutrophil recovery of PSBC HPC, Cord Blood appears comparable to that of the HPC, Cord Blood products that contributed to the docket data and the COBLT study. The median time to platelet recovery seems favorable for PSBC HPC, Cord Blood. However, the incompleteness of the PSBC HPC, Cord Blood data, insufficient information about the nature and severity of the diseases included, the relatively small PSBC HPC, Cord Blood patient dataset, and the lack of characterization of a suitable allograft for some patients are important factors limiting any comparison to the COBLT and Docket data.

Table 2. Hematopoietic Recovery for Patients Transplanted with HPC, Cord Blood Total Nucleated Cell (TNC) Dose ≥2.5 x 10^7/kg

Data Source	The COBLT Study*	Docket* and Public Data*	PSBC HPC, Cord Blood **
Design	Single-arm prospective	Retrospective	Retrospective
Number of patients	324	1299	Variable*
Median age (range)	4.6 (0.07 – 52.2) yrs	7.0 (<1 – 65.7) yrs	35 (0-72) yrs
Gender	59% male 41% female	57% male 43% female	59% male 41% female
Median TNC Dose (range) (x 10^7/kg)	6.7 (2.6 – 38.8)	6.4 (2.5 – 73.8)	3.9 (2.5 – 42.3)
Neutrophil Recovery at Day 42 (95% CI)	76% (71% – 81%)	77% (75% – 79%)	82% (77% - 87%)
Platelet Recovery at Day 100 (20,000/uL) (95% CI)	57% (51% – 63%)	-	66% (60% - 72%)[β]
Platelet Recovery at Day 100 (50,000/uL) (95% CI)	46% (39% – 51%)	45% (42% – 48%)	50% (42% - 59%)
Erythrocyte Recovery at Day 100 (95% CI)	65% (58% – 71%)	-	-
Median time to Neutrophil Recovery	27 days	25 days	21.5 days
Median time to Platelet Recovery (20,000/uL)	90 days	-	46 days
Median time to Platelet Recovery (50,000/uL)	113 days	122 days	53 days
Median time to Erythrocyte Recovery	64 days	-	-

* FDA-1997-N-0010
****** Sample size for median age = 468. N for gender= 468. Median TNC dose n = 194 (from units ≥ 2.5 x 10^7). Neutrophil data n= 339. For ≥20k Platelet n= 328. N for 50k platelet = 267.
[β]Median TNC dose (all doses) = 3.2 x 10^7

The PSBC HPC, Cord Blood data do not include information regarding immunologic reconstitution. However, based on the analyses of the docket data and supported by the public data, HPC, Cord Blood has demonstrated the ability of immunologic reconstitution for patients transplanted for primary immunodeficiency as well as for other malignant and nonmalignant disorders (See Section 12. Appendices).

PSBC HPC, Cord Blood transplantation for hematopoietic and immunologic reconstitution is a potentially life-saving treatment for certain diseases affecting the hematopoietic system; however, the risks are serious and potentially fatal. The safety review of this BLA focuses on transplantation-related adverse events, including early death (defined as Day 100 after transplantation), infusion reactions, graft-versus-host disease (GVHD), and graft failure. The assessment of those adverse events is based primarily on the docket data, supplemented by the PSBC HPC, Cord Blood data (where available), and taking into consideration the publically available data. Table 3

summarizes the frequency of those adverse events in patients who have received a suitable allograft. The incidence of the adverse events of PSBC HPC, Cord Blood is incomplete; however, the data that are available do not identify any safety issues that are atypical for this class of products.

Table 3. Summary of Safety, Frequencies of Major Adverse Events--A Comparison among PSBC HPC, Cord Blood, Docket, and COBLT Data for Patients with a TNC Dose ≥2.5 x 10^7/kg

Adverse Events	*Docket or COBLT	PSBC HPC, Cord Blood
Early Mortality (Day 100)	25% (Docket)	48/212=22.6%
Primary Graft Failure	16% (Docket)	35/203=17.2%
Acute GVHD	69% (Docket)	116/200=58%
Infusion Reactions	65% (COBLT)	22/212=10.3%

*Pooled data from multiple blood banks

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 PSBC HPC, Cord Blood, are not new because they are the same as for HEMACORD—the first FDA-approved HPC Cord Blood product, manufactured by New York Blood Center. Therefore, this application does not trigger PREA.

Although the risks of conducting HPC, Cord Blood transplantation in conjunction with a preparative regimen for hematopoietic reconstitution are high, the diseases that affect the hematopoietic system for which cord blood transplantation is indicated are usually serious or life-threatening. Therefore, the risk-benefit 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 type of hematopoietic progenitor cells.

There are no obvious safety issues related to PSBC HPC, Cord Blood that warrant post-marketing requirements or commitments. However, to monitor the post-marketing safety of the product, the reviewers recommend, and the applicant has agreed to conduct, the following post-marketing surveillance if PSBC HPC, Cord Blood is licensed in the United States:

a. Implement a safety outcomes monitoring and analysis plan. This plan will include: 1) maintenance of an observational database to include, for all Puget Sound Blood Center (PSBC) 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.

b. Submit to FDA a 15-day "alert report" for each serious infusion reaction associated with administration of PSBC HPC, Cord Blood.

Based on overall risk-benefit consideration of the docket data referenced in this application, supplemented by the PSBC HPC, Cord Blood data, and taking into consideration the publically available data, the reviewers recommend approval of PSBC HPC, Cord Blood 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.

However, the risk-benefit assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, characteristics of the graft, and on other available treatment or types of hematopoietic progenitor cells.

Because the risks of PSBC HPC, Cord Blood and its preparative regimen can be mitigated and managed through the labeling of the product and pharmacovigilance plan, the reviewers do not recommend a Risk Evaluation and Mitigation Strategy (REMS), Postmarketing Requirement (PMR), or Postmarketing Commitment (PMC) for PSBC HPC, Cord Blood.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

The proposed indication for this product is 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 risk-benefit 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 categories of disorders for which hematopoietic and immunologic reconstitution is required include malignancies, metabolic disorders, marrow failure, hemoglobinopathy, immunodeficiency, and certain autoimmune disorders. These diseases are usually serious, life-threatening, and with unmet medical needs. Please see the FDA reviews of the docket information for malignant and non-malignant indications regarding the effect of hematopoietic and immunologic reconstitution on specific disease outcomes. (See Section 12. Appendices).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

The FDA-approved therapies for hematological malignancies include various chemotherapy, immunotherapy, and targeted biologic agents. For some non-malignant indications, there are FDA-approved therapies including drugs, biologics, immunotherapy, and other standard supportive therapy. However, there are no FDA-approved, pharmacologically unrelated therapies for hematopoietic and immunological reconstitution as proposed in this BLA.

2.3 Safety and Efficacy of Pharmacologically Related Products

There are several sources of stem cells for allogeneic hematopoietic stem cell transplantation (HSCT), including hematopoietic progenitor cells derived from bone marrow (HPC-M) and hematopoietic progenitor cells derived from peripheral blood apheresis (HPC-A). Use of unrelated cord blood has increased over the past 20 years with improved outcomes. Unrelated cord blood transplantation has extended the availability of allogeneic HSCT to patients who would not be eligible for this potentially curative approach because of lack of an HLA-identical bone marrow (HPC-M) or granulocyte colony-stimulating factor mobilized peripheral blood hematopoietic stem cell (PBSC, HPC-A) donor. Studies suggest that the total number of nucleated cells is the most important factor for engraftment, while favorable outcomes can occur in spite of some degree of HLA mismatch.

FDA has approved five HPC, Cord Blood products for the same indication as in this BLA. The five products are HEMACORD from New York Blood Center, Inc., approved in 2011; HPC, Cord Blood from ClinImmune Labs, approved in 2012; DUCORD from the Carolinas Cord Blood Bank (Duke University School of Medicine), approved in 2012; ALLOCORD from SSM Cardinal Glennon Children's Medical Center, approved in 2013; and HPC, Cord Blood from LifeSouth, approved in 2013.

The PSBC Cord Blood Services product, HPC, Cord Blood is another preparation of HPC, Cord Blood produced under the same regulations and guidances as the five licensed products above.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

In 1996, two groups (Kurtzberg, Laughlin, et al. 1996 and Wagner, Rosenthal, et al. 1996) first reported use of umbilical cord blood as a source of hematopoietic stem cells for transplantation into unrelated recipients. Since then, the clinical use of umbilical cord blood as an alternative source of stem cells has been growing steadily. Over 10,000 unrelated-donor cord blood stem cell transplantations have been performed to date for a variety of diseases and conditions, such as hematological malignancies, immunologic disorders, and inborn errors of metabolism (American Academy of Pediatrics, 2007).

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

06/08/2011	Type B Pre-BLA meeting
06/02/2014	Prior BLA (125556/0) filed
06/16/2014	FDA acknowledgement letter of BLA 125556/0 filing
07/18/2014	FDA issued Refuse To File (RTF) letter for 125556/0
01/15/2015	BLA 125585/0 filed
02/05/2015	FDA receipt acknowledgement letter of BLA 125585/0
03/26/2015	FDA issued acceptance letter for BLA 125558; CMC requested additional information
05/04/2015	Applicant responded to FDA information request (7/18/2014)
11/02/2015	Applicant responded to FDA information request (10/20/2015)

The applicant's first BLA submission (#125556/0) was deficient in manufacturing data. The FDA at that time informed the applicant of the information required to be included in

a BLA, and offered assistance by providing additional suggestions for information to be included in a future BLA submission.

2.6 Other Relevant Background Information

On January 20, 1998 (63 FR 2985), FDA issued a notice in the Federal Register entitled "Request for Proposed Standards for Unrelated Allogeneic Peripheral and Placental/Umbilical Cord Blood Hematopoietic Stem/Progenitor Cell Products; Request for Comments" that FDA proposed to determine if it would be possible to develop product standards and establishment and processing controls for minimally manipulated unrelated allogeneic hematopoietic stem/progenitor cell products intended for hematopoietic reconstitution, based on existing clinical trial data, or data developed shortly thereafter, demonstrating the safety and effectiveness of such cells. Submitted comments were to include supporting clinical and nonclinical laboratory data and other relevant information. A period of two years was provided, until January 20, 2000, for interested persons to submit supporting clinical data. At the request of industry, the comment period was reopened for 90 days until July 17, 2000 (65 FR 20825, April 18, 2000).

On February 27, 2003, the Biological Response Modifiers Advisory Committee (BRMAC) met to discuss issues related to the use of unrelated allogeneic hematopoietic stem/progenitor cells derived from placental/umbilical cord blood for hematopoietic reconstitution, including the analysis of clinical outcome data submitted to FDA as well as information provided by guest experts regarding the safety and effectiveness of cord blood for hematopoietic reconstitution. On the basis of the submitted information, discussion of the BRMAC, and review of published literature on this subject, FDA determined that the data were sufficient to establish the safety and effectiveness of HPC-Cs for allogeneic transplantation in the treatment of hematologic malignancies.

On January 17, 2007 (72 FR 1999), the draft guidance for licensure of minimally manipulated cord blood entitled "Guidance for Industry: Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies" became available. Additional discussion was held with the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) on March 30, 2007. The committee discussed access to HPC, Cord Blood units already in inventory and recommended additional clinical indications. In the process of finalizing the guidance, the FDA considered the recommendations of the CTGTAC, the public comments to the draft guidance, and additional data submissions.

In a Federal Register notice of October 20, 2009 (74 FR 53753), FDA announced the availability of the "Guidance for Industry - Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications". In this notice of availability, the FDA also announced that it would end the period of phased-in implementation of IND and BLA requirements for HPC, Cord Blood. This announcement established a two-year implementation period, which ended October 20, 2011, by which all distribution of HPC, Cord Blood for clinical use in the United States would need to be done under an approved BLA or active IND.

The new, updated final guidance of the same title was issued in March 2014. Among other changes, the indication contained in this guidance differs from the indications listed in the scope of the 2009 licensure guidance. This difference is a result of FDA's re-

examination of the legacy docket data and FDA's consideration of the proceedings of the September 2011 meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

This submission was accepted for filing by the review team because most elements required for review were satisfactory. The BLA was submitted on compact discs (CDs), which were loaded by FDA into the Electronic Document Room (EDR). The applicant did not submit paper copies. The main focus of the clinical and statistical review was the clinical outcome data and adverse events.

The clinical dataset submission consists of data that contained narrative summaries and tables of safety and efficacy outcomes and Microsoft Excel files of the PSBC HPC, Cord Blood data. Due to the voluntary nature of data collection, missing data occur in various degrees for different variables. The major issues related to the data include the following:

Incompleteness

The dataset includes outcome information consisting of neutrophil and platelet recovery, transplantation-related complications, infusion reactions, and mortality. The dataset lacks information on diagnostic criteria for each disease. The dataset does not contain case report forms (CRFs) for any patients, as it is based upon information collected incidentally in the course of the practice of medicine.

Missing Data

Missing data of different degrees have been described under each category of outcome measure.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Good Clinical Practices (GCPs) generally apply to clinical trials. No clinical trials were conducted by the applicant. Therefore, GCPs are not applicable for this BLA.

3.3 Financial Disclosures

The applicant referenced the docket and public data to support this BLA, therefore, the application does not rely on clinical trial data. Consequently, there are no financial disclosures submitted with the application.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Please see Chemistry, Manufacturing, and Controls (CMC) review of this BLA for details.
Donor Information

HPC, Cord Blood donations are screened to exclude potential donors with either a medical history of increased risk of infection or positive screening tests such as HIV, hepatitis, and CMV. Products are also screened for homozygous or double heterozygous hemoglobinopathy. Screens for genetic diseases that could be transmitted through transplantation are conducted through maternal and family medical history questionnaires. PSBC does not exclude women taking antibiotics during labor and delivery, therefore, the labeling needs to warn transplant physicians to monitor for allergic reactions in recipients with history of allergy to certain antibiotics.

Collection Procedures

The clinical reviewer reviewed the collection SOPs. There are no major safety concerns regarding the SOPs.

4.2 Nonclinical Pharmacology/Toxicology

The device components used in manufacturing and storage are cleared by FDA for cord blood processing, and the anticoagulant and diluents are approved by FDA. No additional studies of biocompatibility were required.

Dimethyl sulfoxide (DMSO) represents a potentially toxic component of PSBC HPC, Cord Blood. Published studies report teratogenic responses caused by intraperitoneal administration of DMSO to rodents. Intravenous administration of DMSO to rodents caused hemolysis.

Please see pharmacology/toxicology review of this BLA for details.

4.3 Clinical Pharmacology

4.3.1 Mechanism of Action

Hematopoietic stem progenitor cells from PSBC HPC, Cord Blood migrate to the bone marrow where they divide and mature. The mature cells are released into the bloodstream, where some circulate and others migrate to tissue sites, partially or fully restoring blood counts and function, including immune function, of blood-borne cells of marrow origin. However, the precise mechanism of action is unknown.

In patients with enzymatic abnormalities due to certain severe types of inborn disorders, mature leukocytes resulting from HPC, Cord Blood transplantation may synthesize enzymes that can improve cellular functions of some native tissues. However, the precise mechanism of action is unknown.

4.4 Statistical

The analyses of the PSBC HPC, Cord Blood data are based on a subset of patients, who received a single infusion of PSBC HPC, Cord Blood. Due to the voluntary nature of data collection, missing data occur in various degrees for different variables.

4.5 Pharmacovigilance

The applicant submitted a standard pharmacovigilance plan, and the reviewers determined this is appropriate and sufficient to continue to monitor the safety profile of

PSBC HPC, Cord Blood. In addition, the reviewers do not identify any new safety concerns that are not already known for this class of product. Therefore, the BLA review does not include a Pharmacovigilance Plan Review from the Office of Biostatistics and Epidemiology.

However, a post-marketing safety outcomes monitoring and analysis plan, and expedited reporting of serious infusion reactions, will be useful to monitor the post-marketing safety of the product. The applicant has agreed to a post-marketing safety outcomes monitoring and analysis plan, and will submit post-marketing expedited reporting of serious infusion reactions, as recommended by FDA.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

5.1.1 Scope of Efficacy Review

The efficacy review of PSBC HPC, Cord Blood focuses on its ability of hematopoietic reconstitution based primarily on the docket data, supplemented by the PSBC HPC, Cord Blood data, and taking into consideration the publically available data (including the COBLT Study). Hematopoietic reconstitution is demonstrated by neutrophil and platelet recovery after transplantation. The ability of PSBC HPC, Cord Blood to reconstitute the immune system and erythrocytes can be reliably extrapolated from FDA reviews of the docket and public data (See Section 12. Appendices).

5.1.2 Scope of Safety Review

The safety review focuses mostly on transplantation-related adverse events, including infusion reactions, death within the 100 days after transplantation (100-day mortality), and graft-versus-host disease (GVHD). The safety review is based primarily on the docket data, supplemented by the PSBC HPC, Cord Blood data, and taking into consideration the publically available data. The applicant did not report any cases of engraftment syndrome, malignancies of donor origin, or transmission of serious infection or rare genetic diseases.

5.1.3 Controls

The PSBC HPC, Cord Blood data are collected from uncontrolled clinical experience. The FDA reviews of the docket and public data, which are the primary data to support the efficacy and safety of PSBC HPC, Cord Blood, serve also as references for both efficacy (hematopoietic reconstitution) (See Section 12. Appendices) and safety (transplantation-related adverse events) (See Section 12. Appendices) of this review.

5.1.4 Statistical Considerations

Descriptive statistics is the primary statistical method used in this review. This clinical BLA review is a collaborative review by the clinical and statistical review teams.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following documents serve as the basis for this review:

- BLA 125585 submission, original submission
- FDA reviews of the docket information (FDA- 1997- N- 0010, Legacy Docket number 97N- 0497 and FDA- 2006- D- 0157, Legacy Docket number 06D- 0514)
- FDA review of the COBLT Study (Data available from the National Heart, Lung, and Blood Institute (NHLBI) via its data-sharing portal at https:/biolincc.nhlbi.nih.gov/home/)

The following FDA reviews are included as Appendices:

- Safety Review of Docket and Public Information (Appendix 12.1) – This review contains the primary evidence of efficacy and safety to support this BLA.
- Efficacy Review (Non-Oncology) – Docket and Public Information (Appendix 12.2)
- Efficacy Review (Oncology) – Docket and Public Information (Appendix 12.3)

5.3 Table of Studies/Clinical Trials

The applicant did not conduct any clinical trials to support this BLA. The materials used in this review include primarily the docket data, supplemented by the PSBC HPC, Cord Blood data, and taking into consideration the publically available data. The reviewers are unable to verify the information in the dataset because there are no case report forms (CRFs) for any patients.

5.4 Consultations

None.

5.4.1 Advisory Committee Meeting

On September 22, 2011, the Cellular, Tissue, and Gene Therapy Advisory Committee discussed the BLA for HemaCord, the first-in-class. No Advisory Committee Meeting was held for this BLA because the review team did not identify any novel concerns.

5.4.2 External Consults/Collaborations

None.

5.5 Literature Reviewed

a. American Academy of Pediatrics, 2007, Cord blood banking for potential future transplantation. Pediatrics 119(1): 165-170.

b. Kurtzberg, J, M Laughlin, ML Graham, et al., 1996, Placental blood as a source of hematopoietic stem cells for transplantation into unrelated recipients. N Engl J Med 335:157-166B

c. Wagner, JE, J Rosenthal, R Sweetman, et al., 1996, Successful transplantation of HLA-matched and HLA-mismatched umbilical cord blood from unrelated donors: analysis of engraftment and acute graft-versus-host disease. Blood 8:795-802.

d. Yellowlees, P, C Greenfield, N McIntyre, 1980, Dimethyl sulfoxide-induced toxicity. Lancet 2:1004-1006.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

The applicant did not conduct any clinical trials to study the efficacy or the safety of PSBC HPC, Cord Blood.

7. INTEGRATED OVERVIEW OF EFFICACY

The assessment of efficacy is based primarily on the docket data, supplemented by the PSBC HPC, Cord Blood data, and taking into consideration the publically available data. The data available for review are descriptive. They are voluntarily reported, and records are not always complete. A suitable allograft is defined as ≥2.5x10^7 cells/kg and HLA match 4/6 or more.

Of 537 patients treated with HPC, Cord Blood from the PSBC Cord Blood Services, 290 patients had sufficient data submitted to determine adequacy of the TNC dose administered. Of the 552 units shipped for transplant, 290 patients had sufficient data for reporting the transplant outcomes in reference to adequacy of Total Nucleated Cell (TNC) dose and other factors as described – 303 units included 13 transplants that were double cord transplants. All of the 290 patients received an HLA-matched unit at 4/6 or more. A majority of these patients (212/290) received a suitable allograft.

Transplantation of PSBC HPC, Cord Blood resulted in hematopoietic reconstitution, indicated by neutrophil, platelet and erythrocyte recovery. Hematopoietic recovery varies with the degree of HLA matching and the TNC dose.

The PSBC HPC, Cord Blood data do not include information to evaluate immunologic reconstitution following PSBC HPC, Cord Blood transplantation. However, based on the docket and public data, HPC, Cord Blood has demonstrated a benefit in immunologic reconstitution for patients transplanted for primary immunodeficiency as well as for other malignant and nonmalignant disorders (See Section 12. Appendices).

7.1 Indication

Puget Sound Blood Center (PSBC) 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 risk-benefit 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.

7.1.1 Methods of Integration

Published data and the docket data were reviewed independently and compared to data from PSBC HPC, Cord Blood for this review.

7.1.2 Demographics and Baseline Characteristics

Demographics (for PSBC HPC, Cord Blood)

The demographics of patients with a single infusion of PSBC HPC, Cord Blood are shown in Table 4. The demographics of PSBC HPC Cord Blood appear comparable to that of the HPC, Cord Blood products that contributed to the docket data.

Table 4. Demographic Characteristics of Docket and PSBC HPC Cord Blood Patients

Patient Characteristics	**Docket Patients with a Suitable Allograft* (N=1299)**	**PSBC Patients with a Suitable Allograft* (N=212)**
Median Age (range)	7 (<1-66) yrs	35 (<1-72) yrs
Age Category		
<2yrs	393 (30%)	12 (5.6%)
2-16/17yrs	786 (61%)	68 (31.8%)
>16/17yrs	120 (9%)	133 (62.6%)
Unknown		
Gender		
Male	524 (40%)	125 (59.0%)
Female	389 (30%)	87 (41.0%)
Unknown	386 (30%)	
Ethnicity/Race		
White	573 (44%)	145 (67.8%)
African-American	90 (7%)	8 (3.7%)
Hispanic	129 (10%)	15 (7.0%)
Asian	28 (2%)	37 (17.3%)
Other	14 (1%)	1 (0.5%)
Unknown	465 (36%)	5 (2.3%)
Diagnosis		
Hematologic Malignancies	862 (66%)	184 (86.0%)
Inborn Errors of Metabolism		21 (9.8%)
Immunodeficiency	93 (7%)	
Metabolic Disorders	134 (10%)	
Bone Marrow Failure	95 (7%)	8 (3.7%)
Hemoglobinopathy	8 (0.6%)	
Others	107 (8%)	1 (0.5%)

*Those who received a unit/units having a TNC dose ≥2.5 x 10^7 cells/kg and HLA match 4/6 or more

7.1.3 Subject Disposition

Not Applicable.

7.1.4 Analysis of Primary Endpoint(s)

There is no pre-specified primary endpoint because no clinical trial was conducted. However, this review uses neutrophil and platelet recovery as the indicators of hematopoietic reconstitution.

For patients surviving at least 14 days following cord blood transplantation, primary graft failure is defined as either never achieved ANC >500/μL by Day 42 or death after 14 days without ANC recovery.

Neutrophil and Platelet Recovery

The neutrophil recovery and median time to neutrophil recovery in patients treated with PSBC HPC, Cord Blood who have data available for review appear no worse than the same parameters assessed after treatment with HPC, Cord Blood products that contributed to the docket data, and to those of the COBLT study. The cumulative incidence of platelet recovery and median time to platelet recovery appear better for PSBC HPC, Cord Blood, compared to the docket and COBLT data; however, because of the observational nature of the data, it is difficult to conclude that these results are different than those reported in the docket or from the COBLT study (Table 2 and Table 5).

Table 5. Hematopoietic Reconstitution of PSBC HPC, Cord Blood: Time to, or Cumulative Incidence of, Neutrophil (ANC) and Platelet (PLT) Recovery

Hematopoietic Reconstitution	Description	Outcomes of Subjects with Suitable Allograft*
Time to ANC recovery	Median time (days) to ANC>500 k/uL	21.5 days (range,6-41)
Cumulative Incidence of ANC recovery	ANC>500k/uL by Day 42	82% (77%-87%)
Time to Plt recovery(>20k)	Median time (days) to Plt>20k/uL	46 days (range,14-98)
Cumulative incidence of Plt recovery (>20k)	Plt>20k/uL by Day 100	66% (60%-72%)
Time to Plt recovery (>50k)	Median time (days) to Plt>50k	53 days (range,24-98)
Cumulative incidence of Plt recovery (>50k)	Plt>50k/uL by Day 100	50% (42%-59%)

*There were 275 patients with Hematopoietic Recovery data; 203 of these patients received a Suitable Allograft.

Neutrophil recovery of PSBC HPC, Cord Blood is further described in Table 6. Of all 275 patients with hematopoietic recovery data (whether or not they were recipients of suitable allografts), 225 (81.8%) exhibited neutrophil recovery by Day 42. The median time required for neutrophil recovery within 42 days in patients receiving a suitable allograft was 20 days.

Table 6. Neutrophil Hematopoietic Reconstitution of PSBC HPC, Cord Blood: Time to, or Cumulative Incidence of ANC Recovery

All patients with Hematopoietic Recovery Data		Patients with a Suitable Allograft*
N (Total)	275	203
ANC>500µl by Day 42 (%)	225 (81.8%)	168 (82.8%)
Median time to ANC>500µl by Day 42 (range)	21 days (6-41)	20 days (6-41)
ANC>500µl without time limit (%)	231 (84.0%)	173 (85.2%)
Median time to ANC>500µl without time limit (range)	21 days (6-89)	21 days (6-89)
Graft failure (%)	50 (18.2%)	35 (17.2%)

*****Patients who received a unit having a TNC dose ≥2.5 x 10^7/kg and HLA match 4/6 or more

Graft Failure

Graft failure was reported in 50 (18.2%) cases within the population in the PSBC dataset. The rate of graft failure among patients receiving a suitable allograft was17.2%. (Table 6). The incidence of graft failure by HLA match and TNC dose is shown in Table 7.

Table 7. PSBC HPC, CORD BLOOD: GRAFT FAILURE BY HLA MATCH AND TNC DOSE

HLA Match	TNC Dose (x 10^7/kg)		
	2.5 to <5	5 to <10	>10
4/6	11/70 (16%)	4/14 (29%)	0/4 (0.0%)
5/6	6/49 (12%)	3/14 (28.6%)	2/18 (0.0%)
6/6	2/15 (13%)	1/8 (12.5%)	0/7 (0.0%)

Platelet Recovery

Platelet recovery of PSBC HPC, Cord Blood is described in Table 8. Of 275 patients with hematopoietic recovery data, 188 patients reached at least 20,000/µL platelets by Day 100 and 169 reached at least 50,000/µL platelets by Day 100, following transplantation. Some centers reported the day of achievement of engraftment to 20,000 and 50,000/µL as the same day, suggesting the possibility that the exact day of engraftment was not recorded. The reported median day reported for recovery was similar in all groups.

Table 8. Platelet Hematopoietic Reconstitution of PSBC HPC, Cord Blood: Time to, or Cumulative Incidence of Platelet Recovery

All Patients with Hematopoietic Recovery Data		Patients with a Suitable Allograft
N (Total)	275	
Platelets >20,000/µl by Day 100	188	139
Median time to Plt >20,000/µl (range)	45 days	46 days (14-98)
Platelets >50,000/µl by Day 100	169	129
Median time to Plt >50,000/µl (range)	51 days	53 days (24-98)

Neutrophil Recovery, HLA matching and TNC Dose

Analysis of docket data has indicated that the TNC dose and degree of HLA match are inversely associated with the time to neutrophil recovery (See Section 12. Appendices).

During her review of Dockets of Public Information regarding HPC, Cord Blood, Dr. Donna Przepiorka generated and validated a mathematical model from the pooled dataset to identify patients with delayed engraftment (i.e., exceed the expected upper 95% confidence limit for time to neutrophil recovery) for patients with hematological malignancies and receiving allografts with at least 4 of 6 HLA antigen match and a TNC dose of >2.5 x 10^7 cells/kg.

This model could help to identify whether the efficacy of the PSBC product is different than the efficacy of HPC, Cord Blood in the docket experience. A total of 154 records with suitable allografts (HLA match ≥4/6, dose ≥2.5 x 10^7/kg, transplanted for hematologic malignancies, was found in the joint clinical/statistical review of this BLA application. Of these, 28 (18%) had a missing value ("NA") for the variable, "Days.to.ANC.500". In this review, these 28 records are excluded from the calculation. The calculated 95% limit in the applicant's dataset ranges from 37 to 50 days. Based on application of this model, as described in Appendix 1, to the applicant's dataset, 3 out of the remaining 126 (2.4%) records exceeded the 95% limit. Thus, the efficacy of PSBC HPC, Cord Blood, appears comparable to that of the HPC, Cord Blood products that contributed to the docket information. However, due to the observational nature and incompleteness among the COBLT, Docket, and applicant's dataset, this calculation, by itself, does not definitively demonstrate comparability of the cord bloods. The comparison of hematopoietic recovery for patients transplanted with suitable allograft among COBLT, Docket, and PSBC HPC, Cord Blood, is shown in Table 9.

Table 9. Comparison of Hematopoietic Recovery for Patients Transplanted with Suitable Allograft among COBLT, Docket, and PSBC HPC, Cord Blood Data

Data Source	COBLT Study*	Docket and Public Data*	PSBC HPC, Cord Blood
Design	Single-arm, prospective	Retrospective	Retrospective
Number of Patients	324	1299	Variable**
Median Age (range)	4.6 (0.7-52.2)) yrs	7.0 (<1-65.7) yrs	35 (0-72) yrs
Median TNC Dose (range) ($x10^7$/kg)	6.7 (2.6-38.8)	6.4 (2.5-73.8)	3.9 (2.5-42.3)$^{\beta}$
Neutrophil Recovery by Day 42 (ANC>500/µL) (95% CI)	76% (71%-81%)	77% (75%-79%)	83% (77%-87%)
Platelet Recovery by Day 100 (>20,000/µL)	57% (51%-63%)	--	66% (60%-72%)
Median Time to Neutrophil Recovery	27 days	25 days	21.5 days
Median Time to Platelet Recovery	90 days	--	46 days **

*HPC, Cord Blood from multiple cord blood banks; FDA-1997-N-0010
**Based on Platelet > 20,000/µL
$^{\beta}$Median TNC dose (all doses) = $3.2x10^7$ cells
--Data not available

7.1.5 Other Endpoint(s)

None.

7.1.6 Persistence of Efficacy

The BLA submission does not include data on the duration of the therapeutic effect.

7.1.7 Product-Product Interactions

The BLA submission does not include data regarding the effect of concomitant medications, devices, or therapies on the efficacy of the PSBC HPC, Cord Blood product.

7.1.8 Additional Efficacy Issues/Analyses

None.

7.1.9 Efficacy Conclusions

Based primarily on the docket data, supplemented by the PSBC HPC, Cord Blood data, and taking into consideration the publically available data, PSBC HPC, Cord Blood can function as an alternative source of hematopoietic progenitor cells for hematopoietic and

immunologic reconstitution in patients with diseases affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment (See Section 12. Appendices).

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The applicant did not conduct any clinical trials to assess the safety of PSBC HPC, Cord Blood. The safety analysis of PSBC HPC, Cord Blood is based primarily on the docket data, supplemented by the PSBC HPC, Cord Blood data, and taking into consideration the publically available data.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The applicant did not conduct any clinical trials to evaluate the safety of PSBC HPC, Cord Blood.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Please see Table 4 for the demographic characteristics of the pooled dataset for patients who received any dose of PSBC HPC, Cord Blood. Table 10 describes the exposure of a subset of the safety population to PSBC HPC, Cord Blood.

Table 10. PSBC HPC, Cord Blood Unit Characteristics and Dose Exposure

Unit Characteristics	PSBC, Cord Blood Subjects with TNC≥2.5 x 10^7
Number of Patients	N=214
HLA Match Level	
4/6	95 (44.4%)
5/6	85 (39.7%)
6/6	31 (14.5%)
Not Reported	3 (1.4%)
Processing Method	
Manual	208 (97.2%)
Automated (Sepax)	5 (2.8%)

8.2.3 Categorization of Adverse Events

The safety review focuses on the adverse events that are primarily transplantation-related, including infusion reactions, death within 100 days after transplantation (Day-100 mortality), graft versus host disease (GVHD), engraftment syndrome, malignancies of donor origin, and transmission of serious infection and rare genetic diseases. The incidences of these adverse events are compared, where possible, with those obtained from the safety review of the docket information (See Section 12. Appendices).

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

This is not applicable because no clinical trial was conducted.

8.4 Safety Results

8.4.1 Deaths

Table 11 shows the early mortality (Day 100 mortality) with demographic characteristics for patients who received suitable allograft of PSBC HPC, Cord Blood as compared to docket data of patients with suitable allograft. Younger patients were less likely to experience early death. The gender and race groups appeared to have similar mortality rates with not enough cases reported to indicate significant trends. The rates of death by diagnosis and racial group were similar in the PSBC Cord Blood Services HPC, Cord Blood transplants to those listed in the docket dataset (See Section 12. Appendices).

Table 11. Early Mortality with Demographic Characteristics of PSBC HPC, Cord Blood

	Docket Dataset Patients with TNC ≥ 2.5 x 10^7/kg	**PSBC HPC, Cord Blood Patients with a Suitable Allograft N (%)**	
	Deaths ≤ Day 100, %	**Patient N=212**	**Deaths ≤ Day 100 N=48**
Demographic			
Age			
<2 yrs	22.3%	12	1 (8.3%)
2-16/17 yrs	27.4%	68	13 (19.1%)
≥ 17 yrs	48.6%	134	34 (25.3%)
Gender			
Male	18.1%	112	21 (18.7%)
Female	27.0%	100	23 (23%)
Race/Ethnicity			
Caucasian	22.3%	136	31 (22.8%)
African American	28.9%	8	2 (25%)
Hispanics	18.9%	15	8(53.3%)
Asian	19.4%	32	6 (18.7%)
Other	31.3%	4	--
Unknown		4	1 (25%)
Diagnosis			
Hematologic malignancies	46.5%	171	45 (26.3%)
Inborn error of metabolism	32.0%	21	2 (9.5%)
Primary Immunodeficiency	17.7%	--	--
Bone marrow failure	23.4%	8	1 (12.5%)
Hemoglobinopathy		--	--
Others		1	--

--Data not available

Table 12 shows the causes of death after transplantation. As shown in Table 12, regarding early mortality (death within 100 days after transplantation), the most common primary causes of death for PSBC patients who received a suitable allograft were infection (6.5%), primary disease (4.7%), and organ failure (4.7%). Graft failure was the

primary cause of death in 2.3% of the patients. Available data from the Docket dataset showed that the most common causes of death by Day 100 after transplantation for those who received a TNC ≥2.5 x 10^7/kg were infection (7.8%), organ failure (6.5%) , and return of primary disease (3.0%). The primary cause of death from graft failure in the Docket dataset was 2.5% of the patients. Therefore, the PSBC HPC Cord Blood data show a similar incidence of the primary causes of death as the Docket data.

Table 12. Causes of Death after Transplantation of PSBC HPC, Cord Blood and Docket Dataset

	PSBC Cord Blood Services Dataset				**Docket Dataset**	
	All Patients with graft dose reported N=290		**Patient with a Suitable Allograft N=212**		**Patient with a Suitable Allograft N=1289**	
Causes of Death	**Total Reported** N=47 (50.7%)	**Deaths ≤ Day 100** N=67 (23.1%)	**Total Reported** N=106 (50.0%)	**Deaths ≤ Day 100** N=48 (22.6%)	**Total Reported** N=631 (49%)	**Deaths ≤ Day 100** N=328 (25.3%)
Graft failure (n%)	15 (5 %)	12 (4 %)	6 (2.8 %)	5 (2.3 %)	48 (3.7%)	33 (2.5%)
Organ failure (n%)	20 (6.6%)	12 (4%)	16 (7.5%)	10 (4.7%)	115 (8.9%)	84 (6.5%)
Infection (n%)	30 (9.9%)	17 (5.6%)	24 (11.2%)	14 (6.5%)	170 (13.2%)	101 (7.8%)
GVHD (n %)	11 (3.6%)	2 (0.7%)	7 (3.3%)	1 (0.5%)	72 (5.6%)	39 (3.0%)
Primary disease (n%)	51 (16.8%)	16 (5.3%)	33 (15.4%)	10 (4.7%)	168 (13.0%)	39 (3.0%)
2nd Malignancy (n%)	1 (0.3%)	1 (0.3%)	1 (0.5%)	1 (0.5%)	4 (0.3%)	0
Prior malignancy (n%)	-	-	-	-		
Hemorrhage (n%)	5 (1.7%)	3 (1%)	4 (1.9%)	3 (1.4%)		
Pulmonary toxicity (n%)	10 (3.3%)	5 (1.7%)	7 (3.3%)	4 (1.9%)		
Unknown (n%)	-	-	-	-		
Other (n%)	10 (3.3%)	3 (1%)	8 (3.7%)	2 (0.9%)		

Table 13 shows product characteristics and early mortality in the PSBC dataset. In the Stem Cell Therapeutic Outcome Database (SCTOD) from the Center for International Blood and Marrow Transplant Research (CIBMTR), there is an indication of which units were part of a multiple unit transplant case. In 15 cases, both of the units came from the PSBC Cord Blood Services database, therefore the patients reported on are the number seen by the PSBC HPC, Cord Blood bank (total units minus the number of double cord

transplants from this bank). Product characteristics are reported by the units distributed from the bank.

These data come from the 290 patients for whom this information was provided. Death rates in the 4/6 match group were higher at 38% than the death rates for the better matches, 22% for the 5/6 and 9% in the 6/6 HLA matched group.

Table 13. Early Mortality Interactions with Product Characteristics in the PSBC Dataset

	All Patients with Graft Dose Reported (%), N=290	**Patients with a Suitable Allograft (5%), N=212**
Product Characteristic	**Deaths ≤ Day 100 after Transplantation**	**Deaths ≤ Day 100 after Transplantation**
Single Unit	10 %	10 %
Multiple Units	49 %	29 %
Not Reported	-	-
HLA-Match		
4/6	38 %	26 %
5/6	22 %	17 %
6/6	9 %	6 %
Not Reported	-	-
TNC Dose		
$<2.5 \times 10^7$/kg	21.5 %	-
$\geq 2.5 \times 10^7$/kg	31.6 %	31.6 %

8.4.2 Nonfatal Serious Adverse Events

Primary graft failure

Primary graft failure is defined as survival for at least 14 days and 1) failure to achieve an absolute neutrophil count (ANC) greater than 500/µL by Day 42 after transplantation, or 2) death after 14 days without engraftment. Immunological rejection is the primary cause of graft failure and may be fatal.

The PSBC HPC, Cord Blood allograft database for hematopoietic recovery is available for 275 patients. Of these 275 patients, 203 patients received a suitable allograft; 35 of the 203 (35/203=17.2%) patients experienced primary graft failure. See Table 6.

Infusion Reactions

Infusion reactions are defined as adverse events 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 PSBC HPC, Cord Blood, or bacterial contamination.

Reactions were generally reported to the IND holder, the NMDP's BB-IND 7555, "A Centralized Cord Blood Registry to Facilitate Allogeneic, Unrelated Donor Umbilical Cord Blood Transplantation." The database only captures "serious reactions", Grade 3 or higher. The reaction reports PSBC receives are transmitted through NMDP, the holder of the IND under which the units are distributed. Instructions in the IND are to monitor patients for reactions.

PSBC only received notice of those infusions where an adverse event report (Grade 3 or higher) was submitted. Each event was investigated by PSBC Cord Blood Services to explore whether or not preparation of the HPC, Cord Blood unit contributed to the reaction. Of those reported to PSBC, 22 of the reaction events were in patients with a reported adequate dose (TNC dose ≥2.5 x 10^7/kg). Some of those reactions included multiple signs and or symptoms. The incidence of infusion reactions of PSBC HPC, Cord Blood and the COBLT Study is shown in Table 14. The most frequent infusion reaction in the PSBC HPC Cord Blood dataset was hypertension, 14/22 (63.6%). This was followed in frequency by nausea, 6/22 (25.5%) and chest pain, 4/22 (18.2%). In the COBLT Study, the incidence of hypertension was 48% and 12.7% for nausea. Data for the infusion reaction of chest pain is not provided in the COBLT Study. The distribution of infusion reactions for PSBC HPC Cord Blood is similar to the COBLT study reports.

Table 14. Incidence of Infusion Reactions of PSBC HPC, Cord Blood and the COBLT Study

	PSBC HPC, Cord Blood Total Number of Infusions N=552	**PSBC HPC, Cord Blood Units with a TNC Dose ≥2.5 x 10^7/kg N=212**	**COBLT Infusions with a TNC Dose 2.5 x 10^7/kg**
Number of Infusions with Reported Reactions	**47***	**22**	**Number of Infusions Assessed: N=442**
Signs and symptoms reported: Number (%) of patients with this event			65.4%
Hypertension	26 (55.3%)	14 (63.6%)	48.0%
Hypotension	5 (10.6%)	2 (9.1%)	
Hypoxia	2 (4.3%)	2 (9.1%)	2%
Nausea	12 (25.5%)	6 (27.3%)	12.7%
Headache	1 (2.1%)	1 (4.5%)	
Tachycardia	2 (4.2%)	1 (4.5%)	
Vomiting	4 (8.5%)	2 (9.1%)	14.5%
Chest Pain	7 (14.9%)	4 (18.2%)	
Fever, Chills	3 (6.4%)	-	0.9%
Rigor mild	1 (2.1%)	-	
Hives	3 (6.4%)	-	
Bradycardia	5 (10.6%)	2 (9.1%)	10.4%
SOB	3 (6.4%)	2 (9.1%)	
Other	8 (17%)	5 (22.7%)	

*Infusions with Grade 3 reactions or above were the only ones reported.

Table 15 shows infusion reactions after treatment with PSBC HPC, Cord Blood based on demographic characteristics of PSBC HPC, Cord Blood. Reports from the unit infusions reporting reactions showed that a higher percentage of reactions were reported in the younger patients with 14.3% occurring in the group ≤2 years, 8.6% in the 2 to 17 year old group, and 8.1% in the 17 years or greater group. There were so few patients in the younger age groups in this dataset that it is difficult to draw any conclusions about

reaction rate related to age of the patient. Men and women were affected nearly equally (7.8% male and 9.5% female). Preparative regimens, which may have predisposed patients to reactions, were not standardized.

Racial makeup of the patients reporting infusion reactions did not appear to affect the rate of reported reactions as they were consistent throughout all of the groups. The patients with inborn errors of metabolism showed the highest percentage of reactions (15.4%), followed by bone marrow failure (11.1%) and hematologic malignancies (8%). The numbers of reported patients in each group was small.

Table 15. Infusion Reaction Interactions with Demographic Characteristics of PSBC HPC, Cord Blood

	All Units Transplanted		**Units with a TNC dose >2.5 x 10^7/kg**	
Demographic	**Infusions (552)**	**Reactions (47)**	**Infusions (214)**	**Reactions (22)**
Age				
≤ 2 yrs	28	4 (14.3%)	12	1 (8.3%)
2 – 16 yrs	116	10 (8.6%)	68	6 (8.8%)
>17 yrs≤	408	33 (8.1%)	134	15 (11.2%)
Gender				
Male	321	25 (7.8%)	114	13 (11.4%)
Female	231	22 (9.5%)	100	9 (9%)
Race/Ethnicity				
African American	23	2 (8.7%)	8	2 (25%)
Asian	80	10 (12.5%)	37	4 (10.8%)
Caucasion	309	30 (9.7%)	145	13 (9%)
Hispanic	41	3 (7.3%)	15	2 (13.3%)
Other	5	1 (20%)	4	1 (25%)
Unknown	94	1 (1.1%)	5	-
Diagnosis				
Hematologic malignancies	489	39 (8%)	184	19 (10.3%)
Inborn Errors of Metabolism	39	6 (15.4%)	21	1 (4.8%)
Primary immunodeficiency	-	-	-	-
Bone marrow failure	18	2 (11.1%)	8	2 (25%)
Hemoglobinopathy	-	-	-	-
Others	6	-		-

Table 16 shows infusion reaction interactions with product characteristics of PSBC HPC, Cord Blood. No correlation can be inferred from the product characteristics. However, double cord transplants appear to trend toward more reactions than single cord infusions.

Table 16. Infusion Reaction Interactions with product Characteristics of PSBC HPC, Cord Blood

Product Characteristics	All Units Transplanted N (%)		Units with a TNC Dose >2.5 x 10^7/kg N (%)	
	Infusions (552)	Reactions (47)	Infusions (214)	Reactions (22)
Number of Units				
Single	103	13 (12.6%)	67	4 (6%)
Multiple	257	34 (13.2%)	106	18 (17%)
Not Reported	192	-	41	-
HLA-Match				
4/6	234	16 (6.8%)	95	12 (12.6%)
5/6	240	27 (11.3%)	85	9 (10.6%)
6/6	73	4 (5.5%)	31	1 (3.2%)
Not Reported	5	-	3	-
TNC Dose				
<2.5 x 10^7/kg	89	8 (9%)	-	-
≥ 2.5 x 10^7/kg	214	22 (10.3%)	214	22 (10.3%)
Not Reported	249	17 (6.8%)	-	-

Graft-versus-Host Disease (GVHD)

GVHD is a common complication after unrelated cord blood transplantation, induced by immune T cells in donor cord blood that recognize the recipient as "foreign" and attack the host's body cells. While the donor T-cells can cause undesirable systemic immune reactions, those T-cells can have a desirable graft-versus-tumor effect if the transplantation is used to treat cancer such as leukemias. Acute GVHD is defined as occurring within the first 100 days post-transplant, attacking predominantly liver, skin, mucosa, and gastrointestinal tract. Acute GVHD is classified by severity from grade 1 to 4, with grade 4 carrying a poor prognosis. Chronic GVHD occurs after 100 days post-transplant, involving different immune cell subsets, cytokines, and host targets.

Reporting of GVHD in the PSBC Cord Blood Services dataset was available for 376 patients. Of the 376 patients, 199 had reports of a suitable allograft for their transplant, and 116 of the 200 (58%) patients reported acute GVHD. For comparison, the Docket data shows 369/1182 (31.2%) patients with a TNC dose >2.5 x 10^7/kg with acute GVHD. Table 17 compares the PSBC Cord Blood services dataset to the reports of the Docket data reporting on the same events. The unreported events in the PSBC Cord Blood Services dataset may represent no GVHD or unreported GVHD. It is impossible to distinguish between these situations, based on the data available.

Of the patients with a suitable graft reporting acute GVHD, 58/116 (50%) reported Grade 2 disease, 25/116 (21.6%) reported Grade 3, and 12/116 (10.3%) reported Grade 4. For comparison, the Docket data showed 276/1182 (23.3%) for Grade 2, 149/1182 (12.6%) for Grade 3, 73/1182 (6.2%) for Grade 4. Due to the voluntary nature of data collection, in which missing data occur in various degrees, it is difficult for any conclusions to be drawn.

Table 17. Incidences of Acute GVHD of PSBC HPC, Cord Blood and Docket Data

	Acute GVHD PSBC Cord Blood Services Dataset		Docket data	
	Total reported N = 376	**Patients with a Suitable Allograft N = 199**	**Patients reported (N=1381)**	**Patients with a TNC Dose >2.5 x 10^7/kg (N=1182)**
No	171	83 (42%)*		
Yes	203	116 (58%)*	451 (32.7%)	369 (31.2%)
Unknown	2	-		
Grade				
1	38	20 (17.2%)	347 (25.1%)	315 (26.7%)
2	102	58 (50%)	314 (22.7%)	276 (23.3%)
3	41	25 (21.6%)	176 (12.7%)	149 (12.6%)
4	18	12 (10.3%)	93 (6.7%)	73 (6.2%)
Unknown	4	1 (0.9%)	347 (25.1%)	369 (31.2%)

* 53% of patients with a suitable allograft in the database reported any value for GVHD.

In the PSBC HPC Cord Blood dataset, of the 199 patients who received a suitable allograft, 53 (26.6%) developed chronic GVHD. Of the 76 patients who did not receive a suitable allograft, a slightly higher percentage, 25/76 (32.9%) developed chronic GVHD. See Table 18.

Several risk factors have been reported in the literature for GVHD including CMV serostatus, pre-transplant infection, age (older being more at risk), CD34+ dose, and HLA mismatch. The PSBC Cord Blood Services patients were older than the docket data patients. Therefore, they were more likely to be CMV seropositive and to receive a double cord blood transplant, which is also a risk factor for higher incidence of GVHD.

Table 18. Analysis of Chronic GVHD of PSBC HPC, Cord Blood

		All Patients	**Patients with a Suitable Allograft**	**Patients without a Suitable Allograft**	**Allograft dose not reported**
Total Reported (Yes or No)		376	199	76	101
Of Those Reported	Yes	101 (26.9%)	53 (26.6%)	25 (32.9%)	23 (22.8%)
	Limited	45	22	13	10
	Extensive	55	30	12	13
	Not Indicated	-	-	-	-

Engraftment Syndrome

Engraftment syndrome manifests as unexplained fever and rash in the peri-engraftment period. Patients with engraftment syndrome also may have unexplained weight gain, hypoxemia, and pulmonary infiltrates, in the absence of fluid overload or cardiac disease. If untreated, engraftment syndrome may progress to multiorgan failure and death. The treatment of choice to ameliorate the symptoms is systemic corticosteroids.

No information has been submitted to PSBC Cord Blood Services indicating that any patient has experienced engraftment syndrome. Thus, no information regarding engraftment syndrome was submitted by PSBC. Information on Engraftment Syndrome is based on the docket data, and taking into consideration the publically available data (See Appendix 12.1).

Malignancies of Donor Origin, Transmission of Serious Infection and Rare Genetic Diseases

There is no report of any cases of possible transmission of malignancy, serious infection, or genetic disease from the donor material in the PSBC Cord Blood Services data; this information is based upon the docket data, and taking into consideration the publically available data (See Appendix 12.1).

8.4.3 Study Dropouts/Discontinuations

Not applicable.

8.4.4 Common Adverse Events

Please see section 8.4.2 for details.

8.4.5 Systemic Adverse Events

Please see section 8.4.2 for details.

8.5 Additional Safety Evaluations

None.

8.5.1 Dose Dependency for Adverse Events

Dose dependency for adverse events has been discussed in the safety review of the docket and public information (See Section 12. Appendices). Therefore, this review does not include analysis of dose dependency for adverse events.

8.5.2 Time Dependency for Adverse Events

See 8.4 for analyses of total death and death at Day 100 post transplantation.

8.5.3 Product-Demographic Interactions

See Dr. Przepiorka's review of docket and public information (Appendix 12.1) for analyses of product-demographic interactions regarding safety (graft failure) and efficacy (neutrophil recovery) by age, gender, and race/ethnicity.

8.5.4 Product-Disease Interactions

The BLA submission does not include data to assess the product-disease interactions.

8.5.5 Product-Product Interactions

The BLA submission does not include data to assess any product-product interactions.

8.5.6 Human Carcinogenicity

The BLA submission does not include data regarding human carcinogenicity.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

See Dr. Przepiorka's review of docket and public information (Appendix 12.1) for information on overdose of HPC, Cord Blood products. PSBC did not provide information on overdose of their product. PSBC HPC, Cord Blood prepared for infusion contains dimethyl sulfoxide (DMSO). The maximum tolerated dose of DMSO has not been established, but it is customary not to exceed a DMSO dose of 1 gm/kg/day when given intravenously. Toxic overdose of DMSO has been reported in a subject undergoing autologous HPC – bone marrow transplantation (Yellowlees, Greenfield, et al. 1980). There is no report in the literature of a DMSO overdose related to HPC, Cord Blood transplantation.

The BLA submission does not include data regarding the abuse potential, withdrawal, and rebound of PSBC HPC, Cord Blood.

8.5.8 Immunogenicity (Safety)

PSBC HPC, Cord Blood is an allogeneic cord blood hematopoietic progenitor cell therapy for use in an unrelated recipient. An appropriate preparative regimen using chemotherapy and/or total body irradiation is required for engraftment. As a result, clinical complications related to both immunogenicity and the preparative regimens are major safety concerns. Please see Section 8 of this review for details.

8.5.9 Person-to-Person Transmission, Shedding

Transplantation of PSBC HPC, Cord Blood may result in the development of malignancies of donor origin in the recipient, transmission of serious infection and rare genetic diseases from the donor to the recipient. No such cases were reported in this BLA. Please see Appendix 12.1 for more details.

8.6 Safety Conclusions

Based primarily on the docket data, supplemented by the PSBC HPC, Cord Blood data, and taking into consideration the publically available data, the risks associated with PSBC HPC, Cord Blood transplantation are serious and potentially fatal. The adverse events include early death, infusion reactions, graft versus host disease (GVHD), and graft failure.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

There are no data with PSBC HPC, Cord Blood use in pregnant women to inform a product-associated risk. Animal reproduction studies have not been conducted with PSBC HPC Cord Blood. In the U.S. general population, the estimated background risk

of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

9.1.2 Use During Lactation

There is no information regarding the presence of PSBC HPC, Cord Blood in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PSBC HPC Cord Blood and any potential adverse effects on the breastfed infant from HPC Cord Blood or from the underlying maternal condition.

9.1.3 Pediatric Use and PREA Considerations

PSBC HPC, Cord Blood has been used in pediatric patients with disorders affecting the hematopoietic system that are inherited, acquired, or resulted from myeloablative treatment (See Sections 7 and 8 of this review for more details).

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 PSBC HPC, Cord Blood are not new because they are the same as for Hemacord, manufactured by New York Blood Center. Therefore, this application does not trigger PREA.

9.1.4 Immunocompromised Patients

PSBC HPC, Cord Blood has been used in immunocompromised patients due to either the preparative regimen prior to transplantation or the underlying disease(s). Adverse events associated with its use are discussed in Section 8 of this review.

9.1.5 Geriatric Use

Clinical studies of HPC, Cord Blood (from multiple cord blood banks) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, administration of PSBC HPC, Cord Blood to patients aged 65 and over should be cautious, reflecting their greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

None.

10. CONCLUSIONS

Based primarily on the docket data, supplemented by the PSBC HPC, Cord Blood data, and considering the publically available data, we conclude that PSBC HPC, Cord Blood is capable of hematopoietic and immunologic reconstitution in conjunction with an appropriate preparative regimen. PSBC HPC, Cord Blood can function as an alternative

source of hematopoietic progenitor cells for transplantation to treat diseases affecting the hematopoietic system.

PSBC HPC, Cord Blood transplantation for hematopoietic and immunologic reconstitution is a potentially life-saving treatment for certain diseases affecting the hematopoietic system; however, the risks are serious and potentially fatal. The risks associated with 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 myeloavlative treatment, include early death, infusion reactions, GVHD, and graft failure.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 19 provides a detailed assessment of risk-benefit considerations for PSBC HPC, Cord Blood.

Table 19. Risk Benefit Considerations for PSBC HPC, Cord Blood

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment • Etiology categories include hematological malignancies, metabolic disorders, marrow failure, hemoglobinopathy, immunodeficiency, and autoimmune disorders • Unrelated donor hematopoietic progenitor cell transplantation procedures require potentially toxic preparative regimens in order to achieve hematopoietic and immunologic reconstitution	• Hematological malignancies and marrow failure are life-threatening diseases • Metabolic disorder, hemoglobinopathy , immunodeficiency, and autoimmune disease are a group of serious disorders, and can be life-threatening if severe and at late-stage.
Unmet Medical Need	• Chemotherapy, immunotherapy, and targeted biologic agents have significant adverse event potential • Other therapies include hematopoietic stem cells (HSC) from the sources of HLA-matched related or unrelated bone marrow transplant, HLA-matched related cord blood transplant, or granulocyte colony-stimulating factor mobilized peripheral blood donor • The above HSC sources are limited and HPC, Cord Blood provides wider source of HSC for allogeneic HSC transplant.	• In patients who do not have, or cannot use, available HSC sources from autologous or allogeneic bone marrow or peripheral blood, cord blood is a reasonable option
Clinical Benefit	• A single-arm prospective study (COBLT) and retrospective reviews of an observational database in the dockets and public data have demonstrated the effectiveness of class of HPC, Cord Blood as defined by hematopoietic reconstitution. The total nucleated cell dose and the degree of HLA match were associated with the time to neutrophil recovery • Retrospective analyses of the PSBC HPC, Cord Blood database demonstrated comparable results of hematopoietic reconstitution as compared with the COBLT and Docket data	• HPC, Cord Blood can be effectively used in patients who have disorders affecting the hematopoietic system and who have life-threatening or serious diseases but have failed standard therapy and no available other HSC sources for transplant • The effect of the HPC, Cord Blood is related to the numbers of TNC in the cord blood • HPC, Cord Blood can provide a broader and prompt source of HSC • Effectiveness may vary depending on age of the patients, type and stage of disease, and comorbidity
Risk	Based on Docket and COBLT data, • All cause mortality rate of 30% at 100 days post-transplant as result of infection, primary disease, pulmonary causes, multi-organ failure, and GVHD • Acute GVHD in 69% of population, which may benefit for malignant patients as Graft versus tumor effect • Infusion reactions in 65% of population (COBLT), including hypertension, nausea, vomiting, sinus bradycardia, fever, sinus tachycardia, allergy, hypotension, hemoglobinuria, and hypoxia • Primary Graft failure in 16% of population	• The overall risks of the HPC, Cord Blood transplantation along with a myeloablative preparative regimen can be serious and fatal • Standard approved chemotherapy or biologics should be considered first • If failed standard therapy, other HSC source such as autologous or matched bone marrow or cord blood or peripheral cells should be considered • Type of the disease such as hematological malignancies vs. non-oncological disease, stages of the disease, patient health conditions (age, comorbidities, functional status) should be considered when considering using PSBC HPC, Cord Blood
Risk Management	• The risk of fatal infusion reactions, GVHD, engraftment syndrome and graft failure are addressed in the black box warning of the Prescribing Information for HPC, Cord Blood class • Risks of infusion reactions, malignancies of donor origin, transmission of serious infections or rare genetic disease are addressed under Warning and Precaution of the PI. • Risk/benefit assessment should include analyzing disease type and stage, risk factors, number of the TNC and level of HLA match, other available treatment or types of HSCs. • Post-market: clinical outcome data collection; adverse events reporting: serious and unexpected	Labeling information and post-marketing pharmacovigilance monitoring should suffice for risk management; no REMS or PMR is necessary

11.2 Risk-Benefit Summary and Assessment

Transplantation of PSBC HPC, Cord Blood resulted in hematopoietic reconstitution, indicated by neutrophil and platelet recovery.

Based on the docket data and supported by the publically available data, HPC, Cord Blood has demonstrated the ability to reconstitute the immunologic system in patients transplanted for primary immunodeficiency, as well as for other malignant and nonmalignant disorders (Section 12, Appendices).

PSBC HPC, Cord Blood transplantation for hematopoietic and immunologic reconstitution is a potentially life-saving treatment for certain diseases affecting the hematopoietic system; however, the risks are serious and potentially fatal. The risks associated with PSBC HPC-C include early death, infusion reactions, GVHD, engraftment syndrome, and graft failure. The risk-benefit 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.

11.3 Discussion of Regulatory Options

No major safety and efficacy concerns were identified from the clinical and statistical review to warrant a complete response action for the PSBC HPC, Cord Blood BLA. The overall risks of PSBC HPC, Cord Blood can be mitigated in labeling. There are no unexpected or special risks identified from the BLA review to trigger a REMS, PMC or PMR. A post-marketing plan to monitor for safety, as proposed by the applicant, should be sufficient to monitor the safety of PSBC HPC, Cord Blood.

11.4 Recommendations on Regulatory Actions

The reviewers recommend approval of PSBC HPC, Cord Blood for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with a preparative regimen appropriate for treatment of the patient's disease and for hematopoietic and immunologic reconstitution in patients with hematopoietic system-affecting diseases that are inherited, acquired, or result from chemotherapy and/or radiation intended to treat their disease.

11.5 Labeling Review and Recommendations

The package insert (PI) originally submitted to the BLA and all subsequent amendments related to the label were reviewed. Labeling for HPC, Cord Blood is primarily class labeling. Therefore, the labeling of PSBC HPC, Cord Blood follows the format of labeling of previously approved HPC, Cord Blood products.

11.6 Recommendations on Postmarketing Actions

The risks of PSBC HPC, Cord Blood and its related preparative regimen can be mitigated and managed through the labeling of PSBC HPC, Cord Blood and a post-marketing safety monitoring plan. No unexpected safety issues are identified in this BLA review that warrant post-marketing requirements or commitments. The reviewers do not recommend Risk Evaluation and REMS nor PMR or PMC for PSBC HPC, Cord Blood.

The review team recommended, and the applicant agreed, to do the following:

1. Implement a safety outcomes monitoring and analysis plan. This plan will include a) maintenance of an observational database to include, for all PSBC 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, b) aggregate analyses of interval and cumulative adverse experience reports, and c) 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.

2. Submit a 15-day "alert report" for each serious infusion reaction associated with administration of PSBC HPC, Cord Blood.

12. Appendices

Appendix 12.1 Safety Review: Hematopoietic Progenitor Cells-Cord Blood; Primary Reviewer: Donna Przepiorka, MD, PhD

Appendix 12.2 Clinical Efficacy Review, Nonmalignant Indications: Hematopoietic Progenitor Cells-Cord Blood; Primary Reviewer: John E. Hyde, Ph.D., M.D.

Appendix 12.3 Clinical Efficacy Review, Malignant Indications: Hematopoietic Progenitor Cells-Cord Blood; Primary Reviewer: Maura O'Leary, M.D.