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Division / Office	GMB/DCEPT/OCTGT (Clinical) TEB/DB/OBE (Statistical)
Priority Review	No
Reviewer Name(s)	Clinical reviewer: Mark Borigini, MD (OCTGT) Statistical reviewer: Stan Lin, PhD (OBE)
Review Completion Date / Stamped Date	June 11, 2013
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	LifeSouth Community Blood Centers, Inc.
Established Name	HPC (Hematopoietic Progenitor Cells), Cord Blood
(Proposed) Trade Name	HPC, Cord Blood
Pharmacologic Class	Allogeneic Cord Blood
Formulation	Each Unit of LifeSouth HPC, Cord Blood contains: <ul style="list-style-type: none"> • Active ingredient: a minimum of (b)(4) x 10⁸ total nucleated cells (TNC) with a minimum of 1.25 x 10⁶ viable CD34 cells • Inactive ingredients: dimethyl sulfoxide (DMSO), citrate phosphate dextrose (CPD), hydroxyethylstarch, and Dextran 40.
Dosage Form and Route of Administration	A cell suspension for intravenous use only.
Dosing Regimen	Recommended minimum dose is 2.5 x 10⁷ TNC/kg at time of cryopreservation.

Indication	LifeSouth HPC, Cord Blood is an allogeneic cord blood hematopoietic progenitor cell therapy intended 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.
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GLOSSARY

Table 1. Abbreviations and Glossary

ABO	A human blood type and blood group system
AC	Advisory Committee
Age Group Definition	Neonate: ≤ 28 days; Infant: > 1 month; pediatric: ≥ 1 and < 18 years; Adult: > 18 years; geriatric: ≥ 65 years
AE	Adverse Event
ALL	Acute lymphoblastic leukemia
AML	Acute myelogenous leukemia
ANC	Absolute Neutrophil Count
APLB	Advertising and Promotional Labeling Branch
ARDS	Acute Respiratory Distress Syndrome
BLA	Biologics license application
BRMAC	The Biological Response Modifiers Advisory Committee
CBER	Center for Biologics Evaluation and Research
CBU	Cord Blood Unit
CCBB	Carolinas Cord Blood Bank
CD	Compact Disc
CD34	A cluster of differentiation molecule present on certain cells within the human body
CFR	Code of Federal Regulations
CFU	Colony-forming unit
CI	Confidence interval (95%, unless otherwise specified)
CIBMTR	Center for International Blood and Marrow Transplant research
CMC	Chemistry, manufacturing, and controls
CML	Chronic Myelogenous Leukemia
CMV	Cytomegalovirus
COBLT	The Cord Blood Transplantation Study
CRID	CIBMTR Recipient Identification
CRO	Contract Research Organization
CPD	Citrate-Phosphate-Dextrose
eCTD	Electronic Common Technical Document
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
EBV	Epstein-Barr virus
ES	Engraftment syndrome
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GVHD	Graft versus host disease
HbsAg	Hepatitis B surface antigen

HCV	Hepatitis C Virus
HHV	Human herpes virus
HL	Hodgkins Lymphoma
HLA	Human leukocyte antigen
HPC-A	Hematopoietic progenitor cells, Apheresis
HPC-M	Hematopoietic progenitor cells, Marrow
HSCT	Hematopoietic stem cell transplantation
Kg	Kilogram
IEA	Fanconi Anemia
IIS	Omenn Syndrome
IMD	Hurler Syndrome
IND	Investigational New Drug application
MDS	Myelodysplastic syndrome
MPD	Myeloproliferative disorder
NHL	Non-Hodgkins Lymphoma
NHLBI	National Heart, Lung and Blood Institute
NIH	National Institutes of Health
NHL	Non-Hodgkins Lymphoma
NMDP	National Marrow Donor Program
NRBC	Nucleated Red Blood cells
NYBC	New York Blood Center
OBE	Office of Biostatistics and Epidemiology
OCTGT	Office of Cellular, Tissue, and Gene Therapies
OL	Other Leukemia
PBSC	Peripheral blood stem cells
PCD	Multiple Myeloma
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PDUFA	Prescription Drug User Fee Act
PI	Prescribing Information; Package Insert
PID	Primary immunodeficiency disorder
PK	Pharmacokinetics
PLT	Platelet
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PREA	Pediatric Research Equity Act
REMS	Risk Evaluation and Mitigation Strategy
SAA	Severe Aplastic Anemia
SAE	Serious adverse event
Sepax	Automated cord blood processing technology
SOP	Standard Operating Procedure
Suitable Allograft	TNC dose at $\geq 2.5 \times 10^7/\text{kg}$ and HLA match at $\geq 4/6$
TC	Transplant Center
THAL	Thalassemia

TNC	Total nucleated cells
UCB	Unrelated Cord Blood
VCA IgG	Viral capsid antigen immunoglobulin G
VOD/SOS	Veno-occlusive Disease/Sinusoidal Obstructive Syndrome

1. EXECUTIVE SUMMARY

LifeSouth Community Blood Centers, Inc. applied for biologics licensure of LifeSouth HPC, Cord Blood, a cord blood product manufactured by the applicant. LifeSouth 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 applicant did not conduct any clinical trials to study the efficacy or the safety of LifeSouth HPC, Cord Blood. To support the safety and efficacy of LifeSouth HPC, Cord Blood, the applicant submitted their own dataset (LifeSouth HPC, Cord Blood data) of 81 patients who received allogeneic cord blood units manufactured by LifeSouth Community Blood Centers, Inc., and referenced data in the dockets (FDA-1997-N0010 and FDA-2006-D-0157), as well as published literature related to HPC, Cord Blood.

The efficacy of HPC, Cord Blood, including LifeSouth 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 LifeSouth HPC, Cord Blood is defined by hematopoietic reconstitution of patients who received a suitable cord blood allograft. Transplantation of LifeSouth 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 ($ANC > 500/\mu l$). Platelet recovery is the time from transplantation to a platelet count more than 20,000 per microliter ($> 20,000/\mu l$). 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 LifeSouth 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 LifeSouth HPC, Cord Blood. However, the incompleteness of the LifeSouth HPC, Cord Blood data, insufficient information about the nature and severity of the diseases included, the relatively small LifeSouth 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. Summary of Efficacy, Hematopoietic Reconstitution - a Comparison among LifeSouth HPC, Cord Blood, COBLT and Docket Data (TNC Dose $\geq 2.5 \times 10^7/\text{kg}$)

Data Source	LifeSouth HPC, Cord Blood Patients with Suitable Allograft	COBLT Study	Docket Patients with a TNC Dose $\geq 2.5 \times 10^7/\text{kg}$
	N=22	N=324	N=1299
Neutrophil recovery by Day 42 (95% CI)	91% (71%-98%)	76% (71%-81%)	77% (75%-79%)
PLT recovery by Day 100 (20,000/ μl) (95% CI)	95% (79%-99%)	57% (51%-63%)	--
Platelet recovery by Day 100 (50,000/ μl) (95% CI)	95% (79%-99%)	46% (39%-51%)	45% (42%-48%)
Median time to neutrophil recovery	22 days	27 days	25 days
Median time to platelet recovery (20,000/ μl)	44 days	90 days	--
Median time to platelet recovery (50,000/ μl)	70 days	113 days	122 days

-- Indicates data are not available

The LifeSouth 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).

LifeSouth 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 LifeSouth 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 LifeSouth 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 LifeSouth HPC, Cord Blood, Docket, and COBLT Data**

Adverse Events	*Docket or COBLT	LifeSouth
Early Mortality (Day 100)	25% (Docket)	32%
Primary Graft Failure	16% (Docket)	--
Acute GVHD	69% (Docket)	46%
Infusion Reactions	65% (COBLT)	--

--Indicates data are not available

*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 LifeSouth 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 LifeSouth 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 LifeSouth 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 LifeSouth

- 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 LifeSouth HPC, Cord Blood.

Based on overall risk-benefit consideration of the docket data referenced in this application, supplemented by the LifeSouth HPC, Cord Blood data, and taking into consideration the publically available data, the reviewers recommend approval of LifeSouth 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 his/her characteristics, including the disease itself, specific stage and manifestations of the disease, risk factors, characteristics of the graft, and on the availability of other types of hematopoietic progenitor cells.

Because the risks of LifeSouth 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 LifeSouth 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 blood hematopoietic progenitor cell transplantation procedures for hematopoietic and immunologic reconstitution for diseases affecting hematopoietic systems that are inherited, acquired, or result from myeloablative treatment. 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, 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 three HPC, Cord Blood products for the same indication as in this BLA. The three products are HEMACORD from New York Blood Center, Inc., approved in 2011, HPC, Cord Blood from ClinImmune Labs and DUCORD from the Carolinas Cord Blood Bank, both approved in 2012.

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

12/22/2010	Prior BLA (125412) pre-BLA meeting
11/03/2011	Prior BLA (125412) submission
01/05/2012	Acknowledgement of Withdrawal of BLA 125412 sent to sponsor
05/14/2012	Original BLA (125432) submission

06/25/2012 Conclusion of study (IND 7520), the purpose of which was to establish a public use cord blood bank in accordance with federal and state regulations. The IND was discontinued due to the submission of the BLA.

07/16/2012 BLA (125432) filed

08/24/2012 Response to letter dated 07/16/2012 regarding BLA 125432

09/07/2012 Response to letter dated 08/22/2012 regarding BLA 125432

02/15/2013 Notification to sponsor of major amendment designation

03/22/2013 Notification to sponsor that suggested proprietary name is not acceptable

The applicant's first BLA submission (#125412) was deficient in manufacturing data, and the applicant decided to withdraw the application. The FDA at that time informed the applicant of the minimal filing 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.

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. It consists of four separate volumes. In addition, two CDs were enclosed: one with clinical outcome data (in Excel format); the other includes electronic versions (PDF) of each volume. The main focus of the clinical and statistical review was the clinical outcome data and adverse events.

The dataset submission consists of two electronic discs of data (dated 2011 and 2012, respectively—the latter with additional information not included in the 2011 disc) in the form of Microsoft Excel files, although the applicant states in the submission that this BLA is based on the 2011 dataset. However, the column headings of the data sheets within the files were not defined, therefore limiting the review team’s ability to work with the data sheets to produce summary tables. The reviewers asked the applicant to provide a definition file of these column headings, for each of the Excel sheets within the datasets, and these were provided.

Due to the voluntary nature of data collection, missing data occur in various degrees for different variables, and multiple miscodings and inconsistencies are present within the dataset. The reviewers have attempted to solve these problems with the applicant. 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, 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.

Data Discrepancies

There are multiple discrepancies in the dataset, with enough resolution to allow the completion of this review.

Missing data

Missing data of different degrees have been identified under each category of outcome measure, including HLA matching data.

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, so 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. LifeSouth excludes women taking antibiotics during labor and delivery, so the labeling does not need 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 LifeSouth 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 LifeSouth 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 LifeSouth HPC, Cord Blood data are based on a subset of patients, who received a single infusion of LifeSouth HPC, Cord Blood. Due to the voluntary nature of data collection, missing data occur in various degrees for different variables, and multiple miscodings and inconsistencies are present within the dataset.

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 LifeSouth 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.

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 LifeSouth HPC, Cord Blood focuses on its ability of hematopoietic reconstitution based primarily on the docket data, supplemented by the LifeSouth 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 LifeSouth 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 LifeSouth 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 and rare genetic diseases.

5.1.3 Controls

The LifeSouth 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 LifeSouth 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.

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 125432 submission, including both original submission and subsequent amendments between May, 2012 and December, 2012.
- 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 LifeSouth 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 LifeSouth HPC, Cord Blood.

7. INTEGRATED OVERVIEW OF EFFICACY

The assessment of efficacy is based primarily on the docket data, supplemented by the LifeSouth HPC, Cord Blood data, and taking into consideration the publically available data. Transplantation of LifeSouth 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 LifeSouth HPC, Cord Blood data do not include information to evaluate immunologic reconstitution following LifeSouth 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

LifeSouth 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.

7.1.1 Methods of Integration

Published data and the docket data were reviewed independently and compared to data from LifeSouth for this review.

7.1.2 Demographics and Baseline Characteristics

Demographics

Demographics of patients with a single infusion of LifeSouth HPC, Cord Blood are shown in Table 4. These patients are slightly older than those whose data contributed to the docket information.

Table 4. Demographic Characteristics of LifeSouth HPC, Cord Blood Recipients

		All Subjects
Age(years)	Mean(SD)	28 (22.6)
	Median	21
	Range	0 -- 72
Age Category	Neonate<28days	--
	Infant: 1 – 12 months	7 (10%)
	Pediatric: 1 – <18 years	31 (36%)

		All Subjects
Adult: 18 – <40 years		17 (20%)
Adult: 40 – <65 years		26 (31%)
Geriatric: ≥65 years		2 (2%)
Unknown		--
Gender	Male	27 (51%)
	Female	26 (49%)
	Unkn	--
Ethnicity/Race	African	1 (2%)
	African-American	5 (9%)
	North Am Black Unspecified	1 (2%)
	North American	10 (19%)
	South Asian	1 (2%)
	Western European	1 (2%)
	White South or Central America	2 (4%)
	White Unspecified	32 (60%)
Diagnosis	ALL	17(21%)
	AML	28 (35%)
	CML	4 (5%)
	HL	1 (1%)
	IEA	2 (3%)
	IIS	7 (9%)
	IMD	3 (4%)
	MDS	4 (5%)
	NHL	5 (6%)
	OL	5 (6%)
	PCD	3 (4%)
	SAA	2 (3%)

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/ μ L by Day 42 or death after 14 days without ANC recovery.

Neutrophil and Platelet Recovery

The neutrophil recovery and median time to neutrophil recovery of LifeSouth HPC, Cord Blood patients with recovery data appear no worse than that of 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 seem favorable for LifeSouth HPC, Cord Blood, compared to the docket and COBLT data; however, because of the relatively small number of patients who received LifeSouth HPC, Cord Blood units and because of the incompleteness of the LifeSouth HPC, Cord Blood data, it is difficult to conclude that these results are different than those reported in the docket or from the COBLT study (Table 6).

Table 5. Hematopoietic Reconstitution of LifeSouth HPC, Cord Blood: Time to, or Cumulative Incidence of, Neutrophil (ANC) and Platelet (PLT) Recovery (N=22)

Hematopoietic Reconstitution	Description	Outcomes of Subjects with Suitable Allograft
Time to ANC recovery	Median time (days) to ANC>500 k/uL	22 days
Cumulative Incidence of ANC	ANC>500k/uL by Day100	91%
Time to Plt recovery(>20k)	Median time (days) to	44 days
Cumulative incidence of Plt recovery (>20k)	Plt \geq 20k/uL by Day 100	95% (79%-99%)
Time to Plt recovery (>50K)	Median time (days) to	70 days
Cumulative incidence of Plt recovery (>50K)	Plt \geq 50k/uL by Day 100	95% (79%-99%)

Neutrophil Recovery, HLA matching and TNC Dose

Table 6. Comparison of Hematopoietic Recovery for Patients Transplanted with Suitable Allograft among COBLT, Docket, and LifeSouth HPC, Cord Blood Data

Data Source	COBLT Study*	Docket and Public Data*	LifeSouth
Design	Single-arm, prospective	Retrospective	Retrospective
Number of Patients	324	1299	22
Median Age (years)	4.6	7.0	8
Median TNC Dose ($\times 10^7$ /kg)	6.7	6.4	5.1
Neutrophil Recovery by Day 42 (ANC > 500 μ L)	76%	77%	91%
Platelet Recovery by Day 100 (>20,000/ μ L)	57%	--	95%
Median Time to Neutrophil Recovery	27 days	25 days	22 days
Median Time to Platelet Recovery	90 days	--	44 days**

*HPC, Cord Blood from multiple cord blood banks

**Based on Platelet > 20,000

--Data not available

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 $\geq 2.5 \times 10^7$ cells/kg.

This model could help to identify whether the efficacy of the LifeSouth product is different than the efficacy of HPC, Cord Blood in the docket experience. However, due to the small number of LifeSouth patients fulfilling these criteria, we were unable to apply this model.

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 LifeSouth 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 LifeSouth HPC, Cord Blood data, and taking into consideration the publically available data, LifeSouth 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 LifeSouth HPC, Cord Blood. The safety analysis of LifeSouth HPC, Cord Blood is based primarily on the docket data, supplemented by the LifeSouth 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 LifeSouth 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 LifeSouth HPC, Cord Blood.

Table 7 describes the exposure of a subset of the safety population to LifeSouth HPC, Cord Blood.

Table 7. LifeSouth HPC, Cord Blood Unit Characteristics and Dose Exposure

Unit Characteristics	Subjects with TNC \geq 2.5/kg x 10 ⁷ N (%)
Number of Patients	40

Unit Characteristics		Subjects with TNC \geq 2.5/kg x 10 ⁷ N (%)
*HLA Match Level	3/6	5 (12)
	4/6	13 (31)
	5/6	17 (40)
	6/6	5 (12)
Total TNC Dose x 10 ⁷	Median	131
	Range	13.7 - 988
TNC/kg x 10 ⁷	Median	3.0
	Range	0.26-71
	2.5-<5.0	11 (26)
	5.0-<10.0	12 (29)
	10.0-<20.0	1 (0)
	\geq 20	1 (0)
Storage Time (Days)	Median	--
	Range	--
Processing Method	Manual	--
	Sepax	--

*For multiple-unit recipients, the lowest level of HLA match was chosen

--Data are not available.

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 8 shows the total mortality and early mortality (Day 100) in patients who received any dose of LifeSouth HPC, Cord Blood or suitable allograft.

Table 8. Mortality of LifeSouth HPC, Cord Blood Recipients

	Total Mortality	Mortality by Day 100
--	-----------------	----------------------

Demographics		All Patients N (%)	Patients with Suitable Allograft N (%)	All Patients N (%)	Patients with Suitable Allograft N (%)
Number of Patients		45	22	45	22
Mortality		30 (67)	12 (55)	15 (33)	7 (32)
Age	Mean (SD)	28 (21)	16 (20)	27 (24)	18 (24)
	Median	21	7	19	8
	Range	0.3-72	1-61	1-72	1-61
Age Groups	Neonate (<28 days)	--	--	--	--
	Infant (1-12 months)	2(7)	2(17)	1(7)	1(14)
	Pediatric (1-<18 years)	11(37)	6(50)	6(40)	4(57)
	Young adult (18-<40 years)	7(23)	2(17)	4(26)	--
	Older adult (40-<65 years)	9(30)	2(17)	3(20)	2(29)
	Geriatric (≥65 years)	1(3)	--	1(7)	--
Gender	Male	15 (50)	5 (42)	6 (40)	3 (43)
	Female	15 (50)	7 (58)	9 (60)	4 (57)
	Unknown	--	--	--	--
Ethnicity/Race	African	1 (3)	--	--	--
	African-American	4 (13)	--	3 (20)	--
	North Am Black Unspecified	1 (3)	1 (8)	1 (7)	1 (14)
	North American	6 (17)	2 (17)	2 (13)	1 (14)
	South Asian	1 (3)	1 (8)	1 (7)	1 (14)
	Western European	--	--	--	--
	White South or Central America	1 (3)	1 (8)	--	--
	White Unspecified	17 (57)	7 (58)	8 (53)	4 (57)
Diagnosis	ALL	6 (20)	3 (25)	3 (20)	2 (29)
	AML	11 (37)	4 (33)	7 (47)	3 (43)
	CML	2 (7)	--	--	--
	IIS	2 (7)	2 (17)	--	--
	IMD	1 (3)	1 (8)	1 (7)	1 (14)
	MDS	2 (7)	--	2 (13)	--
	NHL	4 (13)	1 (8)	2 (13)	1 (14)
	OL	1 (3)	--	--	--
	SAA	1 (3)	1 (8)	--	--

As shown in Table 9, the overall death rates in LifeSouth HPC, Cord Blood data appear comparable to that of HPC, Cord Blood products that contributed to the docket data.

Table 9. Comparison of LifeSouth HPC, Cord Blood Mortality Data with Docket Data

Death	Docket N (%)	LifeSouth N (%)
Total Mortality	635/1299 (48.9)	12/22 (55)
Early Mortality (Day 100)	328/1299 (25.3)	7/22 (32)

As shown in Table 10, regarding early mortality (death within 100 days after transplantation), the most common primary causes of death were infection, primary

disease and organ failure. As seen in the Docket data (see Appendix 12.1), the most common (>5%) causes of death by Day 100 after transplantation for those who received a suitable dose ($TNC \geq 2.5 \times 10^7/\text{kg}$) were infection (7.8%) and organ failure (6.5%). Therefore, LifeSouth HPC, Cord Blood data show a similar incidence of the primary causes of death as the Docket data.

Table 10. Primary Causes of Early Death (Day 100) Of LifeSouth HPC, Cord Blood Patients*

Primary Cause of Death	Frequency	Percent
ACUTE GVHD	1	3
ARDS	3	9
BACTERIAL INFECTION	3	9
CHRONIC GVHD	1	3
GRAFT REJECTION/FAILURE	1	3
INTRACRANIAL HEMORRHAGE	1	3
MULTIPLE ORGAN FAILURE	3	9
OTHER ORGAN FAILURE	2	6
ORGANISM_INFECTION	1	3
RECURRENT PRIMARY DISEASE	1	3
RECURRENT_RESIDUAL DISEASE	7	23
RELAPSE/PROGRESSIVE/PERSISTENT DISEASE _	1	3
RENAL FAILURE	1	3
VIRAL INFECTION	2	6
VIRAL--OTHER-PNEUMONIA	1	3
VOD-SOS	1	3

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 greater than 500/ μ L by Day 42 after transplantation, or 2) died after 14 days without engraftment. Immunological rejection is the primary cause of graft failure and may be fatal.

Suitable LifeSouth HPC, Cord Blood allograft information is not available for this analysis.

Infusion Reactions:

Infusion reactions are defined as adverse events occurring within 24 hours of transplantation. The causes of infusion reactions may include reactions to hemolyzed HPC, Cord Blood, allergic or anaphylactic reactions to any component of LifeSouth HPC, Cord Blood, or bacterial contamination. Suitable LifeSouth HPC, Cord Blood allograft information is not available for this analysis.

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 occurs within the first 100 days post-transplant, attacking 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. The frequency of acute GVHD appears less in the LifeSouth HPC, Cord Blood dataset compared to the docket information (Tables 11,12), although suitable allograft information is not available for this analysis.

Table 11 Acute GVHD (Grade 1-4) in LifeSouth HPC, Cord Blood and Pooled Docket Data

Occurrence of Acute GVHD	LifeSouth HPC, Cord Blood Patients (N=53)	Docket Patients with a TNC Dose $\geq 2.5 \times 10^7$/kg (N=1182)
No	28 (54%)	369 (31%)
Yes	25 (46%)	813 (69%)

Table 12. Grade of Acute GVHD in LifeSouth HPC, Cord Blood and Pooled Docket Data

Grade of Acute GVHD	LifeSouth HPC, Cord Blood Patients (N=25)	Docket Patients with a TNC Dose $\geq 2.5 \times 10^7/\text{kg}$ (N=1182)
1	7	315 (27%)
2	10	276 (23%)
3	4	149 (13%)
4	4	73 (6%)

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 regarding engraftment syndrome was submitted by LifeSouth, and thus 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 LifeSouth 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 the 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. LifeSouth did not provide information on overdose of their product. LifeSouth 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 LifeSouth HPC, Cord Blood.

8.5.8 Immunogenicity (Safety)

LifeSouth 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 regimen are major safety concerns. Please see section 8 of this review for details.

8.5.9 Person-to-Person Transmission

Transplantation of LifeSouth 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 LifeSouth HPC, Cord Blood data, and taking into consideration the publically available data, the risks associated with LifeSouth 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

Animal reproduction studies have not been conducted with LifeSouth HPC, Cord Blood. It is also not known whether LifeSouth HPC, Cord Blood can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. There are no adequate and well-controlled studies in pregnant women. LifeSouth HPC, Cord Blood should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

9.1.2 Use During Lactation

The BLA does not include information regarding the safety of using LifeSouth HPC, Cord Blood during lactation.

9.1.3 Pediatric Use and PREA Considerations

LifeSouth HPC, Cord Blood has been used in pediatric patients with disorders affecting the hematopoietic system that are inherited, acquired, or resulted from myeloablative treatment (Please 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 LifeSouth 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

LifeSouth 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 LifeSouth 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 LifeSouth HPC, Cord Blood data, and considering the publically available data, we conclude that LifeSouth HPC, Cord Blood is capable of hematopoietic and immunologic reconstitution in conjunction with an appropriate preparative regimen. LifeSouth HPC, Cord Blood can function as an alternative source of hematopoietic progenitor cells for transplantation to treat diseases affecting the hematopoietic system.

LifeSouth 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 LifeSouth HPC, Cord Blood include early death, infusion reactions, GVHD, and graft failure.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 13 provides a detailed assessment of risk-benefit considerations for LifeSouth HPC, Cord Blood

Table 13. Risk benefit considerations for LifeSouth HPC, Cord Blood

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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. 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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 LifeSouth HPC, Cord Blood database demonstrated comparable results of hematopoietic reconstitution as compared with the COBLT and Docket data 	<ul style="list-style-type: none"> 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	<p>Based on Docket and COBLT data,</p> <ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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 LifeSouth HPC, Cord Blood
Risk Management	<ul style="list-style-type: none"> 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 	<p>Labeling information and post-marketing pharmacovigilance monitoring should suffice for risk management; no REMS or PMR is necessary</p>

11.2 Risk-Benefit Summary and Assessment

Transplantation of LifeSouth 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).

LifeSouth 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 LifeSouth 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 LifeSouth HPC, Cord Blood BLA. The overall risks of LifeSouth 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 LifeSouth HPC, Cord Blood.

11.4 Recommendations on Regulatory Actions

The reviewers recommend approval of LifeSouth 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.

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 LifeSouth HPC, Cord Blood follows the format of labeling of previously approved HPC, Cord Blood products.

11.6 Recommendations on Postmarketing Actions

The risks of LifeSouth HPC, Cord Blood and its related preparative regimen can be mitigated and managed through the labeling of LifeSouth 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 LifeSouth 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 LifeSouth 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 LifeSouth HPC, Cord Blood.