Application Type	Original Application
STN	125413/0
CBER Received Date	October 21, 2011
PDUFA Goal Date	August 20, 2012
Branch / Division / Office	GMB/DCEPT/OCTGT (Clinical), TEB/DB/OBE (Statistical)
Priority Review	No
Reviewer Name(s)	Lei Xu, M.D., Ph.D. (OCTGT) Renee Rees, Ph.D. (OBE)
Review Completion Date / Stamped Date	August 15, 2012
Supervisory Concurrence	Changting Haudenschild, M.D. (Team Leader, OCTGT) Ilan Irony, M.D. (Branch Chief, OCTGT) Wilson Bryan, M.D. (Division Director, OCTGT) Shiowjen Lee, Ph.D. (Team Leader, OBE) Boguang Zhen, Ph.D. (Branch Chief, OBE)
Applicant	SSM Cardinal Glennon Children's Medical Center
Established Name	HPC (Hematopoietic Progenitor Cells), Cord Blood
(Proposed) Trade Name	AlloCORD
Pharmacologic Class	Cord Blood
Formulation(s), including Adjuvants	Has the following ingredients: dimethyl sulfoxide (DMSO) and Dextran 40
Route(s) of Administration	Intravenous
Dosing Regimen	Recommended minimum dose is 2.5×10^7 total nucleated cells (TNC)/kg at cryopreservation.
Indication(s)	AlloCORD is an allogeneic cord blood hematopoietic progenitor cells 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.

GLOSSARY: TABLE OF ABBREVIATIONS

AE	Adverse event
ANC	Absolute neutrophil count
BLA	Biologics License Application
CFR	Code of Federal Regulations
CI	Confidence interval (95%, unless otherwise specified)
COBLT	The Cord Blood Transplantation Study
CMC	Chemistry, Manufacturing, and Controls
CRF	Case report form
DMSO	Dimethyl sulfoxide
GCP	Good Clinical Practice
GVHD	Graft versus host disease
HLA	Human leukocyte antigen
HPC	Hematopoietic progenitor cells
HPC-A	Hematopoietic progenitor cells-apheresis
HPC-M	Hematopoietic progenitor cells-marrow
HSCT	Hematopoietic stem cell transplantation
MPD	Myeloproliferative disorder
MRI	Magnetic resonance imaging
NCBP	National Cord Blood Program
NHLBI	National Heart, Lung and Blood Institute
NMDP	National Marrow Donor Program
PeRC	Pediatric Regulatory Committee
PLT	Platelet
PMC	Post-marketing commitment
PMR	Post-marketing requirement
PREA	Pediatric Research Equity Act
SAE	Serious adverse event
SCTOD	Stem Cell Therapeutic Outcomes Database
SOPs	Standard operating procedures
TNC	Total nucleated cells

LIST OF TABLES

1. EXECUTIVE SUMMARY

SSM Cardinal Glennon Children's Medical Center applies for biologics licensure of AlloCORD[1] (HPC (hematopoietic progenitor cells), cord blood manufactured by the applicant). 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 AlloCORD. To support its BLA, the applicant submitted its own observational dataset (AlloCORD data), and referenced data in the dockets (FDA-1997-N-0010 and FDA-2006-D-0157) and data available from the public domain.

The AlloCORD data include 1086 patients who received a single infusion of a suitable allograft of AlloCORD. A single infusion is defined as infusion of either a unit of AlloCORD or multiple units of AlloCORD on the same day. A suitable allograft is defined as a unit having a total nucleated cell (TNC) dose $\geq 2.5 \times 10^7$/kg and degree of human leukocyte antigen (HLA) match 4/6 or more. The AlloCORD data were collected in the Stem Cell Therapeutic Outcomes Database (SCTOD) by individual transplantation centers.

The efficacy of AlloCORD is defined by hematopoietic reconstitution. The assessment of efficacy is based primarily on the docket data, supplemented by the AlloCORD data, and considering the publically available data, including the Cord Blood Transplantation Study (COBLT Study). Transplantation of AlloCORD resulted in hematopoietic reconstitution, indicated by neutrophil, platelet and erythrocyte 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 to a platelet count more than 20,000 per microliter (> 20,000/μl). Erythrocyte recovery is the time to a reticulocyte count greater than 30,000 per microliter (> 30,000/μl). The docket data demonstrate that the TNC dose and degree of HLA match are inversely associated with the time to neutrophil recovery. Table 1 summarizes the efficacy data. The cumulative incidence of neutrophil recovery of AlloCORD appears comparable to that of the HPC, Cord Blood[2] products that contributed to the docket data and the COBLT study. The cumulative incidence of platelet recovery appears to be better for patients who received AlloCORD than for subjects in the COBLT study. However, the AlloCORD data are incomplete, and the

1 AlloCORD refers to HPC (hematopoietic progenitor cells), Cord Blood manufactured by the applicant (SSM Cardinal Glennon Children's Medical Center) in this review.

2 HPC, Cord Blood refers the class of hematopoietic progenitor cells, which is derived from cord blood and manufactured by different blood banks in this review.

incidence of platelet recovery is based on a relatively small subset of the patients who received AlloCORD. Therefore, the data are insufficient to support a claim of superior effectiveness of AlloCORD.

Table 1 Summary of Efficacy Demonstrated by Hematopoietic Reconstitution

	COBLT Study* Patients with a TNC Dose ≥2.5 x 10^7/kg	**Docket* Patients with a TNC Dose ≥2.5 x 10^7/kg**	**AlloCORD Patients with a Suitable Allograft**
Design	Single-arm prospective	Retrospective	Retrospective
Number of Patients	324	1299	1086**
Median Age	4.6	7.0	6.6
Median TNC Dose	6.7	6.4	6.4
Neutrophil Recovery by Day 42 (ANC>500/μl)	76%	77%	88%
Platelet Recovery by Day 100 (>20,000/μl)	57%	-	87%
Erythrocyte Recovery by Day 100 (> 30,000/μl)	65%	-	-

* HPC, Cord Blood from multiple cord blood banks
** Only a subset of these patients was used in the analysis of neutrophil and platelet recovery and the amount of data missing is different for each variable (See Table 6 for details).

The AlloCORD data do not include information regarding immunologic reconstitution. However, based on the docket, and considering the publically available 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 (Appendices 1, 2 and 3).

AlloCORD 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, infusion reactions, graft versus host disease (GVHD), and graft failure. The assessment of these

adverse events is based primarily on the docket data, supplemented by the AlloCORD data, and considering the publically available data. Table 2 summarizes the frequency of these adverse events. The incidence of adverse events associated with AlloCORD appears similar to the incidence of these events for the HPC, Cord Blood products that contributed to the docket data.

Table 2 Frequencies of Major Adverse Events (AEs) Associated with AlloCORD

Major AEs	AlloCORD Patients with a Suitable Allograft	Docket Patients with a TNC dose $\geq 2.5 \times 10^7$/kg
Early Death (Day-100 mortality)	17%	29.8%
Infusion Reactions	8.9%	
Acute GVHD	51%	63%
Chronic GVHD	20%	
Primary Graft Failure	12%	16.4%

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

There are no safety issues related to AlloCORD that warrant post-marketing requirements (PMR) or post-marketing commitments (PMC). 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 AlloCORD 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 AlloCORD 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 AlloCORD"

Based on overall risk-benefit consideration of the docket data referenced in this application, supplemented by the AlloCORD data, and consiering the publically available data, the reviewers recommend approval of AlloCORD 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.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

HPC, Cord Blood has been used as a source of hematopoietic progenitor cells for transplantation to treat a variety of diseases affecting the hematopoietic system, such as hematological malignancies, hematological non-malignant disorders, primary immunodeficiency, and inborn errors of metabolism. Please see the FDA reviews of the docket information for malignant and non-malignant indications regarding the effect of hematopoietic and immunologic reconstitution on the specific disease outcomes. (Appendices 1, 2 and 3)

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

There are several sources of stem cells for allogeneic transplantation, including hematopoietic progenitor cells derived from bone marrow (HPC-M) and hematopoietic progenitor cells derived from peripheral blood apheresis (HPC-A). The choice of HPC source for allogeneic transplantation is individualized for each patient and depends on several factors, including donor availability, human leukocyte antigen (HLA)-matching, and overall risk-benefit assessment.

2.3 Safety and Efficacy of Pharmacologically Related Products

Two HPC, Cord Blood products have been licensed in the United States, including HemaCord from New York Blood Center, Inc., and HPC, Cord Blood from ClinImmune Labs for the same indications as proposed in this BLA.

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 using 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 error of metabolism (American Academy of Pediatrics, 2007).

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

06/17/2010	Pre-BLA meeting
10/21/2011	**Original BLA submission**
12/1/2011	A.1 – Modified submission, a sample of patient dataset was included
12/20/2011	**BLA filed**
1/13/2012	A.3 – Partial response to letter 12/20/2011
4/30/2012	Submission of the patient dataset in response to 04/04/2012 teleconference
5/3/2012	Re-submission of the patient dataset, in response to 4/30/2012 teleconference

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

The applicant submitted raw AlloCORD data in an Excel format that included outcome information submitted to the Stem Cell Therapeutic Outcomes Database (SCTOD) by individual transplantation centers. The dataset includes 1819 patients, who received 1964 units of AlloCORD between 1996 and October 2011. Among these patients, 1230 patients received a single infusion of AlloCORD and have available information on TNC dose and HLA matching status. A summary of the subsets of data available for analysis is shown in Table 3.

The overall quality of the AlloCORD data is acceptable for review. However, 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. However, the dataset lacks information on diagnostic criteria for each disease. The dataset does not contain case report forms (CRFs) for any patients.

Data Discrepancies

There are multiple discrepancies in the dataset – particularly in neutrophil recovery data. In general, cases with obvious errors are excluded from data analyses in this review.

Missing data

Missing data of different degrees have been identified under each category of outcome measure (Table 3). For example, over half of the patients are missing hematopoietic data.

Table 3 Development of Safety and Efficacy Data Subsets for Analyses

Step	Data file subset	Number of Patients
1	Submitted data file	1819 patients with 1964 units
	1a. And limited to transplants with only *all* SLCBB units (dual cord transplants with one product from another manufacturer are removed)	1272 patients with 1416 units
	1b. And limited to units reported as "being infused" (some units were reported in the dataset as "not infused" to some patients, without providing a reason)	1248 patients with 1388 units
	1c. And limited to records with TNC/kg dose *and* HLA match reported (Note: these records all include age or gender)	1230 patients with 1369 units
	1d. If a patient received multiple units on the same day; the multiple units were combined to one infusion with the TNC doses summed up.	1230 patients with 1257 infusions
2	**Subsets in this step are used for analysis of infusion reactions**	
	2a. Step 1d data file limited to records with infusion reaction data	104 patients with 104 infusions
	2b. And limited to patients with a suitable allograft*	98 patients with 98 infusions
3	**Subsets in this step are used for analysis of death and GVHD**	
	3a. Step 1d data file limited to the first transplanted unit for patients with multiple transfusion dates	1230 patients with infusions
	3b. And limited to patients with a date of death or last contact	567 patients
	3c. And limited to patients with a suitable allograft	501 patients
4	**Subsets in this step are used for analysis of hematopoietic recovery**	
	4a. Step 3b data file limited to patients with hematopoietic recovery	509 patients
	4b. And limited to patients with a suitable allograft	449 patients

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

Collections were performed at 33 sites in the states of Missouri, Illinois, and Kansas from 1996 to 2011. Staff (obstetricians and/or midwives) at each site were responsible for obtaining maternal consent, reviewing medical records, collecting the cord blood (ex utero), and coordinating transportation of the cord blood, and associated documents. No in utero collections are performed.

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

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 AlloCORD. 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 AlloCORD 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.

4.4 Statistical

The analyses of the AlloCORD data are based on a subset of patients, who received a single infusion of AlloCORD. 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; the reviewers determined that this plan is appropriate and sufficient to continue to monitor the safety of

AlloCORD. In addition, the reviewers have not identified 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 (Please see section 11.5 of this review for details).

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 AlloCORD focuses on hematopoietic reconstitution, based primarily on the docket data, supplemented by the AlloCORD 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 AlloCORD to reconstitute the immune system and erythrocytes relies on FDA reviews of the docket and public data (Appendices 1, 2 and 3).

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 motility), and graft versus host disease (GVHD). The safety review is based primarily on the docket data, supplemented by the AlloCORD data, and considering 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 AlloCORD 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 AlloCORD, serve also as references for both efficacy (hematopoietic reconstitution) (Appendices 1, 2 and 3) and safety (transplantation-related adverse events) (Appendix 1) 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 125413 submission, including both original submission and subsequent amendments between November 2011 and May 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 1) – This review contains the primary evidence of efficacy and safety to support this BLA.
- Efficacy Review (Oncology) – Docket and Public Information (Appendix 2)
- Efficacy Review (Non-Oncology) – Docket and Public Information (Appendix 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 AlloCORD data, and considering the publically available data. Each transplantation center reports its own outcome data to the Stem Cell Therapeutic Outcomes Database (SCTOD), where the applicant obtained the AlloCORD data. The applicant did not receive any serious adverse event (SAE) reports directly from any transplantation centers. 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 (if applicable)

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 AlloCORD.

7. INTEGRATED OVERVIEW OF EFFICACY

The assessment of efficacy is based primarily the docket data, supplemented by the AlloCORD data, and considering the publically available data, Transplantation of AlloCORD 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 AlloCORD data do not include information to evaluate immunologic reconstitution following AlloCORD transplantation. However, based on the docket data, and considering the and the publically available 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 (Appendices 2 and 3).

7.1 Indication

AlloCORD 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

The data submitted by the applicant include 1819 patients, who received 1964 units of AlloCORD between 1996 and October 2011. Among these patients, 1086 patients received a single infusion of a suitable allograft. The analyses of AlloCORD data to support the indication of hematopoietic reconstitution were based on the subset of patients who received a single infusion of suitable allograft of AlloCORD. The dataset

has no information regarding each transplantation center. Therefore, no center-specific analysis was performed.

7.1.2 Demographics and Baseline Characteristics

Demographics

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

Table 4 Demographic Characteristics

Patients Characteristics	**AlloCORD Patients with a Suitable Allograft (N=1086)**	**Docket Patients with a TNC dose ≥2.5 x 10^7/kg (N=1299)**
Median Age (Range)	6.6 yrs (19 d -70yrs)	7 yrs (<1-66 yrs)
Age Groups	Neonate (<1 month) 5 (0.46%) Pediatric (1 month – <18 yrs) 856 (79%) Adult (18 - < 65 yrs) 214 (20%) Geriatric (≥ 65 yrs) 8 (0.74%) Unknown 3 (0.28%)	<2 yrs 393 (30%) 2 – 17 yrs 786 (61%) ≥17 yrs 120 (9%)
Female Male Unknown	464 (43%) 585 (54%) 37 (3.4%)	389 (30%) 524 (40%) 386 (30%)
Caucasian Hispanic African-American Asian American Indian Multi-Race Unknown	578 (53%) 99 (9.1%) 72 (6.6%) 19 (1.7%) 1 (0.092%) 6 (0.55%) 311 (29%)	573 (44%) 129 (10%) 90 (7%) 28 (2%) 14 (1%) 465 (36%)
Malignancies Immunodeficiency Metabolic Disorders Bone Marrow Failure Hemoglobinopathy Others	750 (69%) 112 (10%) 80 (7.4%) 55 (5.1%) 46 (4.2%) 43 (3.9%)	862 (66%) 93 (7%) 134 (10%) 95 (7%) 8 (0.6%) 107 (8%)

Product Characteristics

Major characteristics of AlloCORD units are summarized in Table 5.

The median TNC dosage and HLA matching status of AlloCORD appears comparable to those of the HPC, Cord Blood products that contributed to the docket information.

Table 5 AlloCORD Unit Characteristics

	AlloCORD Patients with a Suitable Allograft (N=1086)	**Docket Patients with a TNC dose ≥2.5 x 10^7/kg (N=1299)**
TNC Dose/kg		
Median (x 10^7)	6.4	6.4
Range (x 10^7)	2.5 – 67	2.5- 73.8
HLA Matching		
6/6	180 (17%)	143 (11%)
5/6	508 (47%)	524 (40%)
4/6	398 (37%)	583 (45%)
2-3/6	0	40 (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.

Primary graft failure is defined for patients surviving at least 14 days as either never achieved ANC > 500/μl by Day 42 or death after 14 days without ANC recovery.

Neutrophil and Platelet Recovery

Neutrophil and platelet recovery was assessed for the subset of these patients who received a single infusion of suitable allograft of AlloCORD (Table 6).

The cumulative incidence of neutrophil recovery, and the median time to neutrophil recovery, associated with AlloCORD appear comparable to these outcomes for HPC, Cord Blood products that contributed to the docket data, and for the COBLT study. The cumulative incidence of platelet recovery and median time to platelet recovery appear to be better for patients who received AlloCORD than for subjects in the COBLT study. However, the AlloCORD data are incomplete, and the incidence of platelet recovery and the median time to platelet recovery are based on a relatively small subset of the patients who received AlloCORD. Therefore, the data are insufficient to support a claim of superior effectiveness of AlloCORD. The incidence of primary graft failure of

AlloCORD appears comparable to that of the HPC, Cord Blood products that contributed to the docket data.

Table 6 Neutrophil and Platelet Recovery

Data Source	AlloCORD Patients with a Suitable Allograft		COBLT Study Patients with a TNC Dose ≥2.5 x 10^7/kg	Docket Patients with a TNC Dose ≥2.5 x 10^7/kg
	N*		N=324	N=1299
Neutrophil recovery by Day 42 (95% CI)	442	88% (85% -91%)	76% (71%-81%)	77% (75%-79%)
PLT recovery by Day 100 (20,000/μl) (95% CI)	365	87% (83% -91%)	57% (51%-63%)	-
Platelet recovery by Day 100 (50,000/μl) (95% CI)	335	79% (73% -83%)	46% (39%-51%)	45% (42%-48%)
Median time to neutrophil recovery	442	21 days	27 days	25 days
Median time to platelet recovery (20,000/μl)	365	48 days	90 days	-
Median time to platelet recovery (50,000/μl)	335	56 days	113 days	122 days
Primary graft failure	449	12%		16.4%

* The amount of data missing was different for the different variables; therefore, the number of patients (N) is different for each variable.

The docket data review team developed a multivariate logistic regression model starting with the factors significant on a preliminary univariable analysis when analyzing the causes of neutrophil engraftment failure in the docket information. The final model identified diagnosis, degree of HLA mismatch, and TNC dose group as significantly associated with primary graft failure (Appendix 1). The model is most appropriately applicable to hematologic malignancies, as this is the largest subgroup with sufficient homogeneity to examine how these factors (degree of HLA mismatch and TNC dose group) affect engraftment or failure to engraft.

The reviewers of this BLA applied the model using 287 patients who received AlloCORD. These patients were selected from the dataset using the criteria of 1) HLA matching >3/6; 2) TNC dose ≥ 2.5x10^7/kg; 3) transplanted for treating hematologic malignancy; and 4) neutrophil recovery achieved. Thirteen patients (4.5%) had neutrophil

recovery time that exceeded the expected upper 95% confidence limit. This percentage of patients who had excessive days to neutrophil recovery is similar to the percentage in the docket data (4.6%). Based on application of this model to the applicant's dataset, the efficacy of AlloCORD appears comparable to that of the HPC, Cord Blood products that contributed to the docket information.

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 (Appendix 1). Neutrophil recovery was further analyzed in patients with and without a suitable allograft of AlloCORD (Table 7). Due to the small number of patients in the three HLA alleles mismatched (3/6) group, the association between a suitable allograft and the rate of neutrophil recovery cannot be demonstrated.

Table 7 Neutrophil Recovery by HLA Matching and TNC Dose in AlloCORD Data

	TNC Dose ($x10^7$ / kg)			
HLA Match	**<2.5**	**2.5 - < 5.0**	**5.0 - < 10.0**	**≥ 10.0**
3/6	1/1 (100%)	1/1 (100%)	0/1 (0%)	0/0
4/6	13/23 (57%)	57/72 (79%)	47/52 (90%)	29/34 (85%)
5/6	23/28 (82%)	49/59 (83%)	66/79 (84%)	58/67 (87%)
6/6	4/6 (67%)	16/18 (89%)	26/30 (87%)	31/38 (82%)

7.1.5 Other Endpoints

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 use of concomitant medications, devices, or therapies on the efficacy of the AlloCORD.

7.1.10 Additional Efficacy Issues/Analyses

None

7.1.11 Efficacy Conclusions

Based primarily on the docket data, supplemented by the AlloCORD data, and considering the publically available data, we conclude that AlloCORD 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 Appendices1, 2 and 3).

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The applicant did not conduct any clinical trials to assess the safety of AlloCORD. The safety analysis of AlloCORD is based primarily on the docket data, supplemented by the AlloCORD data, and considers 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 AlloCORD.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Please see Table 4 for the demographics of the safety population.

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 (Appendix 1).

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

The overall death rate of AlloCORD appears comparable to that of HPC, Cord Blood products that contributed to the docket data (Appendix 1). The main causes of death include primary diseases, infection, pulmonary failure, organ failure (other than pulmonary failure), GVHD, and graft failure (Table 8).

Early death is defined as death within 100 days post-transplantation (Day-100 mortality). The Day-100 mortality rate of AlloCORD appears to be better for patients who received AlloCORD than for subjects in the docket database. However, the AlloCORD data are incomplete, and the incidence of platelet recovery is based on a relatively small subset of the patients who received AlloCORD. Therefore, the data are insufficient to support a claim of superior effectiveness of AlloCORD (Appendix 1) (Table 8).

Table 8 Death Rate and Cause of Death

Death Rate and Cause of Death	AlloCORD Patients with a Suitable Allograft (N=501)	Docket Patients with a TNC Dose ≥2.5 x 10^7/kg (N=1572)
Death Rate	214 (43%)	838 (53.3%)
Primary Cause of Death		
Primary disease	87 (43%)	
Infection	51 (25%)	(7.8%)
Pulmonary	18 (9%)	
Organ failure	24 (12%)	(6.5%)
GVHD	14 (7%)	
Graft Failure	7 (3%)	(3.7%)
Secondary malignancy	2 (1%)	
Intracranial hemorrhage	3 (1%)	
Unknown	8 (4%)	
Day-100 mortality	85 (N=499)* (17%)	469 (29.8%)

*Transplantation date information is missing for two patients

8.4.2 Nonfatal Serious Adverse Events

Infusion Reactions

Infusion reactions are defined as events likely associated with AlloCORD infusion and occurring within 24 hours after initiation of AlloCORD infusion.

Of note, there is no information in one third of patients about whether they experienced any infusion reactions (Table 9).

Adverse infusion reactions that were reported for at least 5% of patients include hypertension, vomiting, shortness of breath, and bradycardia (Table 10). Some patients were reported to have more than one type of infusion reaction. The transplant centers did not grade the severity of these infusion reactions. The types and frequency of the infusion reactions from the COBLT study are also listed in the table for comparison. In general, the data from AlloCORD and the COBLT study are comparable.

Table 9 Occurrence of Infusion Reactions

Occurrence of Infusion Reactions	AlloCORD Patients with a Suitable Allograft (1086 patients with 1106 infusions*)
No	639 (58%)
Yes	98 (8.9%)
Unknown	369 (33%)

* A small number of patients received more than one unit of AlloCORD on the same day.

Table 10 Types of Infusion Reactions

Infusion Reactions	AlloCORD Patients with a Suitable Allograft (98 infusions with 114 infusion reactions*)	COBLT Study Patients with a TNC Dose $\geq 2.5 \times 10^7$/kg (442 patients)
Hypertension	62 (54%)	46.5%
Vomiting	14 (12%)	15.7%
Shortness of breath	10 (8.8%)	1.7%
Bradycardia	7 (6.1%)	10.3%
Nausea	5 (4.4%)	14.8%
Chest pain	2 (1.8%)	
Hemoglobinuria	2 (1.8%)	1.9%
Fever	2 (1.8%)	5.5%
Hives	2 (1.8%)	
Unknown	2 (1.8%)	
Hypotension	1 (0.88%)	2.9%
Hypoxia	1 (0.88%)	2.9%
Chills	1 (0.88%)	1.3%
Headache	1 (0.88%)	
Dizziness	1 (0.88%	
Rash	1 (0.88%)	
Tachycardia	0	5.2%

* Some infusions reported to have more than one type of infusion reaction.

Graft versus Host Disease (GVHD)

Acute GVHD is defined as GVHD occurring before 100 days post-transplantation. The frequency of acute GVHD appears similar in the AlloCORD dataset and the docket information (Table 11).

Thirty-six percent (36%) developed grades 2-4 GVHD, and 14% developed grades 3-4 GVHD. The proportion of patients by grade is similar in the AlloCORD dataset and the docket information (Table 12).

Chronic GVHD occurs after 100 days post-transplantation and can last for a lifetime. Incidence of chronic GVHD is shown in Table 13 .

Table 11 Occurrence of Acute GVHD (Grade 1-4)

Occurrence of Acute GVHD	AlloCORD Patients with a Suitable Allograft (N=501)	Docket Patients with a TNC Dose ≥2.5 x 10^7/kg (N=1182)
No	190 (38%)	369 (31%)
Yes	257 (51%)	813 (63%)
Unknown	54 (11%)	

Table 12 Grade of Acute GVHD

Grade of Acute GVHD	AlloCORD Patients with a Suitable Allograft (N=501)	Docket Patients with a TNC Dose ≥2.5 x 10^7/kg (N=1182)
1	74 (14%)	315 (27%)
2	110 (22%)	276 (23%)
3	46 (9.2%)	149 (13%)
4	26 (5.2%)	73 (6%)
Not evaluable	1* (0.2%)	

* Number of patients not evaluable due to lack of information on grade

Table 13 Occurrence of Chronic GVHD

Occurrence of Chronic GVHD	AlloCORD Patients with a Suitable Allograft (N=501)
No	340 (68%)
Yes	100 (20%)
Unknown	61 (12%)

Engraftment Syndrome

Engraftment syndrome is an inflammatory condition during neutrophil recovery after hematopoietic stem cell transplantation (HSCT). The applicant did not report any cases of engraftment syndrome.

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.

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 (Appendix 1). Therefore, this review does not include analysis of dose dependency for adverse events.

8.5.2 Time Dependency for Adverse Events

The BLA submission does not include data regarding time dependency for adverse events.

8.5.3 Product-Demographic Interactions

The BLA submission does not include data regarding the product-demographic interactions.

8.5.4 Product-Disease Interactions

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

8.5.5 Product-Product Interactions

The BLA submission does not include data regarding 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

There has been no experience with overdose of any HPC, Cord Blood products in human clinical trials. Single doses of AlloCORD up to 6.7 x 10^8 TNC/kg have been administered. AlloCORD 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 AlloCORD.

8.5.8 Immunogenicity (Safety)

AlloCORD 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 AlloCORD 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. Please see Appendix 1 for more details.

8.6 Safety Conclusions

The risks associated with AlloCORD 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 AlloCORD. It is also not known whether AlloCORD 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. AlloCORD 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 AlloCORD during lactation.

9.1.3 Pediatric Use and PREA Considerations

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

AlloCORD has been used in immunocompromised patients due to either 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 AlloCORD 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 AlloCORD data, and considering the publically available data, we conclude that AlloCORD is capable of hematopoietic and immunologic reconstitution in conjunction with an appropriate preparative regimen. AlloCORD can function as an alternative source of hematopoietic progenitor cells for transplantation to treat diseases affecting hematopoietic system.

AlloCORD 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 AlloCORD include early death, infusion reactions, GVHD, and graft failure.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

A risk-benefit assessment is often complex and requires perspective on a broad range of issues, including (but not limited to), the state of the science, adequacy of the studies/clinical trials reported, the requested indication, treatment alternatives, type and

severity of adverse events, and regulatory precedents. Table 14 documents the risk-benefit considerations for this BLA.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• AlloCORD transplantation can be used to treat disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment. • Many of these disorders are serious and have limited treatment options.	• More treatment options of disorders affecting the hematopoietic system are needed.
Unmet Medical Need	• HPC-M and HPC-A are other stem cell sources for allogeneic HSCT. • Neither HPC-M nor HPC-A is readily available. • HPC, Cord Blood has several potential advantages, such as ready availability and increased HLA disparity in terms of successful engraftment and decreased risk of GVHD, compared to adult HPC-M and HPC-A.	• There is inadequate supply of stem cells for allogeneic HSCT. AlloCORD has potential to help address this unmet medical need.
Clinical Benefit	• Review of data from the applicant, along with docket and public information, support the conclusion that AlloCORD can function as an alternative source of stem cell for HSCT to reconstitute the hematopoietic and immune system. • May be life-saving for some diseases	• AlloCORD can function as an alternative source of stem cells for allogeneic HSCT to reconstitute hematopoietic and immunologic system. • HPC-C has demonstrated the ability in immunological reconstitution for patients transplanted for primary immunodeficiency as well as for other malignant and nonmalignant disorders (Appendices 2, and 3).
Risk	• The most substantial risks of AlloCORD include death, infusion reactions, GVHD, and graft failure. • The incidences of these serious adverse events are similar to the incidences documented in the safety review of the docket (Appendix 1).	• Risks are well-known and serious for AlloCORD, and are the same as for other HPC, Cord Blood of the class. (Appendix 1).
Risk Management	• Current practice, e.g., HLA matching, minimum TNC dose	• Patient selection, as described in label. • Recommended dose. • The applicant has agreed to conduct postmarketing surveillance if AlloCORD is approved (section 11.6 for details). • No safety issues were identified to warrant PMC or PMR.

Table 14 Risk-Benefit Considerations of AlloCORD

11.2 Risk-Benefit Summary and Assessment

Transplantation of AlloCORD resulted in hematopoietic reconstitution, indicated by neutrophil, platelet and erythrocyte 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 (Appendices 2, and 3).

AlloCORD 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 AlloCORD include early death, infusion reactions, GVHD, 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 Recommendations on Regulatory Actions

The reviewers recommend approval of AlloCORD 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.

11.4 Labeling Review and Recommendations

Labeling for HPC, Cord Blood is a class labeling. Therefore, the labeling of AlloCORD will follow the labeling of approved HPC, Cord Blood products.

11.5 Recommendations on Postmarketing Actions

There are no safety issues that warrant PMR or PMC. To continue monitoring the safety of AlloCORD, the reviewers recommend, and the applicant has agreed to conduct the following postmarketing surveillance if AlloCORD is licensed in the United States:

a. Implement a safety outcomes monitoring and analysis plan. This plan will include:
    I. maintenance of an observational database to include, for all 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,
    II. aggregate analyses of interval and cumulative adverse experience reports,
    III. safety outcome 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 a 15-day "alert report" for each serious infusion reaction associated with administration of HPC, Cord Blood. "

12. APPENDICES

- 12.1 Appendix 1: Clinical Safety and Statistical Joint Review – Dockets and Public Information

12.2 Appendix 2: Clinical Efficacy Review – Malignant Indications – Docket and Public information

12.3 Appendix 3: Clinical Efficacy Review – Nonmalignant Indications – Docket and Public Information

3.