

BLA Clinical Review Memorandum

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Applicant	StemCyte, Inc.
Established Name	HPC, Cord Blood
(Proposed) Trade Name	RegeneCyte
Pharmacologic Class	Allogeneic Cord Blood
Formulation(s), including Adjuvants, etc.	Each unit contains: <ul style="list-style-type: none"> Active ingredient: a minimum of 9×10^8 total nucleated cells (TNC) with at least 1.25×10^6 viable CD34 cells at the time of cryopreservation Inactive ingredients: 10% dimethyl sulfoxide (DMSO), 1% Dextran 40
Dosage Form and Route of Administration	Intravenous
Dosing Regimen	2.5×10^7 total nucleated cells (TNC)/kg at cryopreservation
Indication(s) and Intended Population(s)	RegeneCyte, HPC (Hematopoietic Progenitor Cell), 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.
Orphan Designated	No

TABLE OF CONTENTS

GLOSSARY	1
1. EXECUTIVE SUMMARY	2
1.1 Demographic Information: Subgroup Demographics and Analysis Summary	4
1.2 Patient Experience Data	4
2. CLINICAL AND REGULATORY BACKGROUND.....	5
2.1 Disease or Health-Related Condition(s) Studied	5
2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)	5
2.3 Safety and Efficacy of Pharmacologically Related Products	6
2.4 Previous Human Experience with the Product (Including Foreign Experience)	6
2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission	6
2.6 Other Relevant Background Information	7
3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES	8
3.1 Submission Quality and Completeness	8
3.2 Compliance With Good Clinical Practices And Submission Integrity.....	8
3.3 Financial Disclosures	8
4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	9
4.1 Chemistry, Manufacturing, and Controls	9
4.2 Assay Validation	9
4.3 Pharmacology/Toxicology	9
4.4 Clinical Pharmacology	9
4.4.1 Mechanism of Action	9
4.4.2 Human Pharmacodynamics (PD).....	9
4.4.3 Human Pharmacokinetics (PK)	9
4.5 Statistical	9
4.6 Pharmacovigilance	10
5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW	10
5.1 Review Strategy	10
5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review.....	11
5.3 Table of Studies/Clinical Trials	11
5.4 Consultations	11
5.4.1 Advisory Committee Meeting (if applicable)	11
5.4.2 External Consults/Collaborations	11
5.5 Literature Reviewed (if applicable).....	12
6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS	12
7. INTEGRATED OVERVIEW OF EFFICACY	12
7.1 Indication	13
7.1.1 Methods of Integration.....	13
7.1.2 Demographics and Baseline Characteristics.....	13
7.1.3 Patient Disposition.....	15
7.1.4 Analysis of Primary Endpoint(s)	15
7.1.5 Analysis of Secondary Endpoint(s)	16
7.1.6 Other Endpoints.....	17
7.1.7 Persistence of Efficacy	17

7.1.9 Product-Product Interactions	17
7.1.10 Additional Efficacy Issues/Analyses	17
7.1.11 Efficacy Conclusions	17
8. INTEGRATED OVERVIEW OF SAFETY	17
8.1 Safety Assessment Methods	17
8.2 Safety Database	17
8.2.1 Studies/Clinical Trials Used to Evaluate Safety	17
8.2.2 Overall Exposure, Demographics of Pooled Safety Populations	18
8.2.3 Categorization of Adverse Events	18
8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials	18
8.4 Safety Results	18
8.4.1 Deaths	18
8.4.2 Nonfatal Serious Adverse Events.....	20
8.4.3 Study Dropouts/Discontinuations	23
8.4.4 Common Adverse Events.....	23
8.4.5 Systemic Adverse Events.....	23
8.5 Additional Safety Evaluations	23
8.5.1 Dose Dependency for Adverse Events	23
8.5.2 Time Dependency for Adverse Events	23
8.5.3 Product-Demographic Interactions.....	23
8.5.4 Product-Disease Interactions	23
8.5.5 Product-Product Interactions	23
8.5.6 Human Carcinogenicity	24
8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound	24
8.5.8 Immunogenicity (Safety).....	24
8.6 Safety Conclusions	24
9. ADDITIONAL CLINICAL ISSUES	24
9.1 Special Populations	24
9.1.1 Human Reproduction and Pregnancy Data.....	24
9.1.2 Use During Lactation	25
9.1.3 Pediatric Use and PREA Considerations	25
9.1.4 Immunocompromised Patients	25
9.1.5 Geriatric Use	25
9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered	25
10. CONCLUSIONS	25
11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS	26
11.1 Risk-Benefit Considerations	26
11.2 Risk-Benefit Summary and Assessment.....	29
11.3 Discussion of Regulatory Options	29
11.4 Recommendations on Regulatory Actions	29
11.5 Labeling Review and Recommendations	30
11.6 Recommendations on Postmarketing Actions	30
12. APPENDIX.....	30

GLOSSARY

AE	adverse event
aGVHD	acute graft versus host disease
ANC	absolute neutrophil count
BLA	biologics license application
BRMAC	Biological Response Modifiers Advisory Committee
CFR	Code of Federal Regulations
cGVHD	chronic graft versus host disease
CIBMTR	Center for International Blood & Marrow Transplant Research
CMC	chemistry, manufacturing, and controls
COBLT	cord blood transplantation study
CRF	case report forms
CTGTAC	Cellular, Tissue, and Gene Therapies Advisory Committee
DMSO	dimethyl sulfoxide
ES	Executive Summary
FDAAA	Food and Drug Administration Amendments Act of 2007
GVHD	graft versus host disease
HLA	human leukocyte antigen
HPC	hematopoietic progenitor cell
HSCT	hematopoietic stem cell transplantation
NDA	new drug application
PBSC	peripheral blood hematopoietic stem cell
PD	pharmacodynamics
PI	package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PSA	prostate-specific antigen
RCR	red cell reduced
REMS	risk evaluation and mitigation strategy
RMS/BLA	regulatory management system for the biologics license application
RTF	refuse to file
SAE	serious adverse event
SCID	severe combined immunodeficiency disease
SCTOD	Stem Cell Therapeutic Outcomes Database
TNC	total nucleated cells
UCB	umbilical cord blood
UCBT	umbilical cord blood transplant

1. Executive Summary

StemCyte, Inc. (the Applicant) submitted an original biologics license application (BLA) for RegeneCyte¹, a hematopoietic progenitor cell (HPC), cord blood product, on January 7, 2022. The proposed indication and dosage are as follows:

- Indication: 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.
- Dosage: The recommended minimum dose is 2.5×10^7 nucleated cells/kg at cryopreservation. Matching for at least four of six HLA-A antigens, HLA-B antigens, and HLA-DRB1 alleles is recommended.

The product is volume- and red blood cell-reduced allogeneic unrelated umbilical cord blood called HPC, Cord Blood. HPC, Cord Blood contains a minimum of 9×10^8 nucleated cells in a 25 ml mixture of 10% Dimethyl sulfoxide (DMSO) and 1% Dextran 40.

FDA issued a complete response to the original BLA submission, on January 20, 2023, due to chemistry, manufacturing, control (CMC) deficiencies. The Applicant resubmitted the application under Amendment 35 on November 9, 2023.

This BLA contains data from a retrospectively collected observational dataset that includes 54 patients who received a suitable allograft² of RegeneCyte. Clinical trials were not conducted with RegeneCyte. However, the efficacy of HPC, Cord Blood for hematopoietic reconstitution has been previously established through FDA analyses of the pooled data from multiple cord blood banks in the FDA docket (FDA-1997-N-0010; legacy docket number 1997N-0497) as well as the Cord Blood Transplantation (COBLT) Study [NCT00000603].

Efficacy was primarily evaluated through hematopoietic reconstitution as measured by neutrophil and platelet recovery as per the American Society for Transplantation and Cellular Therapy definition (Kharfan-Dabaja MA, et al. 2021). For this BLA review, a suitable allograft was considered to have $\geq 2.5 \times 10^7$ /kg total nucleated cells (TNC) of recipient weight and $\geq 4/6$ degree of human leukocyte antigen (HLA) match. Among the 54 patients in the Applicant's observational dataset, the cumulative incidence of neutrophil recovery defined as the first of three successive days with an absolute neutrophil count (ANC) greater than 500 cells per microliter ($ANC > 500/\mu L$), by Day 42 was 91% as compared to 77% for the pooled docket dataset and 76% in the COBLT study.

¹ RegeneCyte refers to Human Progenitor Cells (HPC), Cord Blood manufactured by the Applicant (StemCyte, Inc.) in this review.

² A suitable allograft was defined as $\geq 2.5 \times 10^7$ /kg total nucleated cells (TNC) of recipient weight and $\geq 4/6$ degree of human leukocyte antigen (HLA) match

Additional measures of hematopoietic reconstitution were also evaluated. The median time from transplantation to an absolute neutrophil count (ANC) greater than 500 cells/ μ L was 22 days, as compared to 25 days in the docket dataset and 27 days in the COBLT study. The incidence of platelet recovery by Day 100, defined as the first of three consecutive days with a platelet count of 20,000 cells/ μ L or higher in the absence of platelet transfusion for 7 consecutive days, was 72%, and the median time from transplantation to a platelet count greater than 20,000 cells/ μ L was 50 days.

Neutrophil and platelet recovery with RegeneCyte appears comparable to the docket data and confirms the efficacy of the product. The Applicant's dataset serves as supportive data to supplement the primary evidence of effectiveness for HPC, Cord Blood that has previously been demonstrated by the docket data and the COBLT study.

During FDA's prior review of the docket data and the publicly available data, we concluded HPC, Cord Blood's ability for immunologic reconstitution in patients who undergo unrelated donor hematopoietic progenitor cell transplantation for primary immunodeficiency as well as for other malignant and nonmalignant disorders ([Appendix](#)). RegeneCyte data do not include information regarding immunologic reconstitution, however, based on the similarity of the available data it is reasonable to conclude a similar effect with this product.

The safety review of this BLA focused on transplantation-related adverse events (AEs) reported in the Applicant's dataset. Major adverse events associated with RegeneCyte include death prior to Day 100 (13.0%), infusion reactions (7.4%), graft versus host disease (66.7%), and graft failure (9.3%). The incidence of AEs associated with RegeneCyte appears comparable to the incidence of these AEs in the pooled data from multiple cord blood banks that contributed to the docket and public data.

There are no safety issues related to RegeneCyte that warrant either a postmarketing requirement (PMR) or postmarketing commitment (PMC) study or a Risk Evaluation and Mitigation Strategy (REMS). The Applicant will conduct routine pharmacovigilance in accordance with 21 CFR 600.80. Postmarketing surveillance for the HPC, Cord Blood product class also includes the implementation of a safety outcomes monitoring and analysis plan as per FDA Guidance for Industry: Biologics License Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System (2014).

Conclusions of safety and effectiveness of RegeneCyte rely on FDA's previous determination of safety and effectiveness for HPC, Cord Blood, which has been demonstrated by the FDA docket data and the COBLT study, and with additional support from RegeneCyte data from 54 patients. Like other HPC, Cord Blood products, RegeneCyte is a potentially life-saving product for certain diseases affecting the hematopoietic system, and it has risks that are serious and can be fatal. Based on overall benefit-risk consideration of the docket and published data referenced in this application, supplemented by the RegeneCyte data, the FDA clinical and statistical reviewers recommend approval of RegeneCyte 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.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The median age of patients was 37.5 years, ranging from 0.1 to 70.3 years. There were 15 pediatric patients, including 5 patients < 2 years of age. There were 26 (48.1%) males and 28 (52.9%) females. There were 17 (31.5%) White, 21 (38.9%) Hispanic, and 9 (16.7%) Black or African American patients. Most patients in the RegeneCyte dataset had hematologic malignancies (44 patients, 81.5%). The detailed demographics of the patient population in the RegeneCyte dataset, including a comparison to the docket data, are provided in [Table 1](#), Section 7.1.2.

1.2 Patient Experience Data

This submission did not include patient experience data and FDA is unaware of any patient perspective/experience studies relevant to review of this submission.

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Patient-reported outcome	
<input type="checkbox"/>	Observer-reported outcome	
<input type="checkbox"/>	Clinician-reported outcome	
<input type="checkbox"/>	Performance outcome	
<input type="checkbox"/>	Patient-focused drug development meeting summary	
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies	
<input type="checkbox"/>	Other: (please specify)	
<input checked="" type="checkbox"/>	If no patient experience data were submitted by Applicant, indicate here.	

Check if Considered	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Perspectives shared at patient stakeholder meeting	
<input type="checkbox"/>	Patient-focused drug development meeting	
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Other stakeholder meeting summary report	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Other: (please specify)	

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 referenced in the [Appendix](#).

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

There are several types of stem cells that may be used in allogeneic transplantation. In addition to HPC, Cord Blood, these include 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.

Currently there are 8 licensed HPC, Cord Blood products:

1. HEMACORD [STN 125397], manufactured by New York Blood Center.
FDA approval: 2011
2. HPC, Cord Blood [STN 125391], manufactured by ClinImmune Labs (University of Colorado Cord Blood Bank)
FDA approval: 2012
3. DUCORD [STN 125407], manufactured by Carolinas Cord Blood Bank (Duke University School of Medicine).
FDA approval: 2012
4. ALLOCORD [STN 125413], manufactured by SSM Cardinal Glennon Children's Medical Center.
FDA approval: 2013
5. LifeSouth HPC, Cord Blood [STN 125432], manufactured by LifeSouth Community Blood Centers.
FDA approval: 2013
6. HPC, Cord Blood [STN 125585], manufactured by Bloodworks.
FDA approval: 2016
7. CLEVECORD [STN 125594], manufactured by Cleveland Cord Blood Center.
FDA approval: 2016
8. HPC, Cord Blood [STN 125657], manufactured by MD Anderson Cord Blood Bank.
FDA approval: 2018

The Applicant's product is another preparation of HPC, Cord Blood produced under the same regulations and guidance documents and for the same indication as these licensed products.

2.3 Safety and Efficacy of Pharmacologically Related Products

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 with some degree of HLA mismatch (Rafiee, 2021). Since initial approval in 2011 of HPC, Cord Blood manufactured by New York Blood Center, seven HPC, Cord Blood products have been approved with well characterized safety and efficacy ([Appendix](#)).

In prior approvals, the incidence of adverse events that are primarily transplantation-related include infusion reactions (65.4%), death within 100 days after transplantation (25%), graft versus host disease (69%), and transmission of serious infection (13%) and have been compared, where possible, with those obtained from the safety review of the docket information. The risk of engraftment syndrome was compared to data from the COBLT study (15%) as this adverse event was not addressed in the docket dataset. The assessment of efficacy is based primarily on the docket data demonstrating hematopoietic reconstitution as defined by neutrophil recovery by day 42 (77%) and platelet recovery to 50,000/ μ L by day 100 (45%). Therefore, even with limited data, we recommend approval based on a favorable evaluation of the benefits and risks associated with this product and product class.

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

In 1996, two groups (Kurtzberg, Laughlin, et al. and Wagner, Rosenthal, et al.) first reported use of umbilical cord blood as a source of hematopoietic stem cells for transplantation (HSCT) into unrelated recipients. Since then, the clinical use of umbilical cord blood as an alternative source of stem cells has been growing steadily. Twenty-five years after the first HSCT with cord blood, more than 35,000 HSCTs have been performed by using cord blood as the source of stem cells worldwide. Published disease distributions were 57% for malignancies, 32.5% for hemoglobinopathies, 6% for severe combined immunodeficiency disease (SCID) or related T-lymphocyte disorders, and 1.5% for other disorders (American Academy of Pediatrics, 2017).

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

January 7, 2022	Original BLA 125764/0 submission
March 8, 2022	Original BLA filed
January 20, 2023	Complete Response letter issued
May 9, 2023	Unofficial meeting to discuss complete response
November 9, 2023	BLA 125764/0.34 resubmission
February 12, 2024	Mid-Cycle meeting
May 10, 2024	Targeted Action Date

Reviewer Comment: The Applicant resubmitted this biologic licensing application on November 9, 2023 following Complete Response due to CMC deficiencies issued during the original submission on January 20, 2023. The clinical recommendation for the original BLA was approval. No new clinical data have been submitted with this resubmission.

2.6 Other Relevant Background Information

On January 20, 1998, 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* (63 FR 2985) which explained that it may 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. To provide a scientific basis for the proposed standards, FDA requested the submission of comments proposing establishment controls, process controls, and product standards designed to ensure the safety and effectiveness of minimally manipulated unrelated allogeneic hematopoietic stem/progenitor cell products derived from peripheral and cord blood for hematopoietic reconstitution. 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 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 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, 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 (72 FR 1999). 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 on 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 ending on October 20, 2011, by which time all distribution of HPC, Cord Blood for clinical use in the United States would need to be done under an approved BLA or active IND.

The new, updated final *Guidance for Industry: Biologics License Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended*

for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System, was issued in March 2014 and included updates resulting from FDA's re-examination of the legacy docket data and FDA's consideration of the proceedings of the September 2011 CTGTAC meeting. This guidance contains information about the manufacture of minimally manipulated, unrelated allogeneic placental/umbilical cord blood and how a manufacturer can obtain a biologics license for their cord blood product.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The RegeneCyte data were submitted by the Applicant as an information amendment in BLA 125764/12. The data reviewed for this BLA were in Excel format and included information submitted to the Stem Cell Therapeutic Outcomes Database (SCTOD) by individual transplantation centers. The dataset includes 54 patients who received a suitable allograft (TNC $\geq 2.5 \times 10^7/\text{kg}$ and $\geq 4/6$ HLA match) with the Applicant's HPC, Cord Blood. Due to the retrospective and voluntary nature of data collection, the following limitations were present:

Incomplete and missing data

RegeneCyte data included outcome information consisting of neutrophil and platelet recovery, transplantation-related complications, and mortality. However, the dataset did not include diagnostic criteria for diseases that comprised the primary indication for transplantation.

Data discrepancies and uncertainties

There were no major data discrepancies identified. Minor discrepancies and miscoding of platelet competing risk values were resolved with the Applicant during the course of the initial review cycle. There was a lack of standardization of data collection and reporting for the voluntarily collected retrospective dataset from the publicly available data from the Stem Cell Therapeutic Outcomes Database.

Reviewer Comment: Effectiveness of HPC, Cord Blood has been previously concluded from the docket data and the COBLT study. The RegeneCyte data are supportive. Therefore, despite the limitations of RegeneCyte data including small sample size, missing data and lack of standardization of the data collection, the RegeneCyte data provide supportive evidence of effectiveness and safety. In this review, the RegeneCyte data are compared to either docket or COBLT data, determined by whichever dataset provide appropriate comparisons and more complete data for the parameter(s) of interest.

3.2 Compliance with Good Clinical Practices and Submission Integrity

No clinical trials were conducted by the Applicant. Good clinical practices are not applicable to this submission as they generally apply to clinical trials.

3.3 Financial Disclosures

The Applicant referenced both docket and public data to support this BLA and 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

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. Initially, umbilical cord blood was processed using a (b) (4) in the final product. In 2012, processing transitioned to a volume and red cell reduced process, where (b) (4). Current manufacturing uses (b) (4) products; therefore, only this data is reviewed for safety and efficacy of this minimally manipulated unrelated allogeneic umbilical cord blood product.

FDA issued a Complete Response letter on January 20, 2023, for the original BLA submission due to Chemistry, Manufacturing, and Controls (CMC) concerns. The CMC concerns included inadequate information on donor testing and screening, viability assays, flow cytometry assay, process validation, and stability studies. StemCyte responded to the Complete Response letter comments and subsequently addressed all items during this review cycle.

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

4.2 Assay Validation

Not applicable

4.3 Pharmacology/Toxicology

The Applicant referenced both docket and public data to support this BLA and did not provide any animal data to support this submission, which is acceptable given the available clinical data in the docket and from the COBLT study.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

This product consists of HPCs collected from cord blood donors for intravenous infusion. Hematopoietic stem progenitor cells 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. However, the precise mechanism of action is unknown.

4.4.2 Human Pharmacodynamics (PD)

Not applicable

4.4.3 Human Pharmacokinetics (PK)

Not applicable

4.5 Statistical

The data analyses are based on a subset of 54 patients who received a suitable allograft (TNC $\geq 2.5 \times 10^7/\text{kg}$ and $\geq 4/6$ HLA match) with at least one unit of RegeneCyte. Due to the voluntary nature of data collection, there were missing data for different outcome

variables. Overall mortality, ANC and platelet recovery data were gathered by the Applicant. Limitations imposed by the lack of standardization of data collection in outcome variables were primarily related to reporting of adverse infusion reactions. Nonetheless, the supporting data provided in this BLA were acceptable to further characterize the benefit:risk profile of previously approved HPC, Cord Blood produced under the same regulations and guidance documents and for the same indication as the licensed products.

The statistical reviewer verified that analyses cited by the Applicant were supported by the submitted data.

Reviewer Comment: The assessment of efficacy is based primarily on the FDA docket data, and the publicly available data, including the COBLT Study. The RegeneCyte dataset is only supportive, therefore, the impact of the missing data is less critical.

4.6 Pharmacovigilance

The Applicant submitted a routine pharmacovigilance plan, which is adequate to monitor the risks associated with RegeneCyte. The available data do not suggest a safety signal that would trigger a Risk Evaluation and Mitigation Strategy (REMS), a postmarketing commitment (PMC) or a postmarketing requirement (PMR) study. The Applicant will conduct routine pharmacovigilance and adverse event reporting in accordance with 21 CFR 600.80, including 15-day expedited reporting for serious and unexpected adverse events and submission of periodic safety reports (Periodic Adverse Experience Reports (PAERs)) at quarterly intervals, for 3 years after licensure, and annually thereafter. (Please see section 11.6 of this review for details).

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

5.1 Review Strategy

Cord blood transplant related products were first approved in 2011. In addition to safety and efficacy docket data, the ability of HPC, Cord Blood to reconstitute hematopoiesis after transplantation is demonstrated in the COBLT Study. Therefore, according to the FDA Guidance for Industry: *Biologics License Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System (2014)*, retrospective data as supportive evidence is adequate, since RegeneCyte is considered a minimally manipulated product and the safety and efficacy has been established for several products of the same drug class as listed in section 2.2.

5.1.1 Scope of Efficacy Review

The efficacy review is based primarily on historical FDA review of the docket data and the publicly available data (including the COBLT Study) and supplemented by the Applicant's data. Hematopoietic reconstitution is demonstrated by neutrophil and platelet recovery after transplantation. The ability of RegeneCyte to reconstitute the immune system and erythrocytes can be reliably extrapolated from FDA reviews of the docket and public data ([Appendix](#)).

5.1.2 Scope of Safety Review

The safety review focuses on transplantation-related AEs, including infusion reactions, death within the first 100 days after transplantation (100-day mortality) and graft versus

host disease (GVHD). The safety review is based primarily on the docket data, publicly available data (including the COBLT Study) and supplemented RegeneCyte data.

5.1.3 Controls

The FDA review of the docket and public data, which provide the primary evidence to support the safety and efficacy of HPC, Cord Blood product class, including RegeneCyte, serve also as references for both efficacy (hematopoietic reconstitution) and safety (transplantation-related adverse events) of this review ([Appendix](#)). RegeneCyte data are considered supportive and are collected from uncontrolled clinical experience.

5.1.4 Statistical Considerations

Descriptive statistical analyses are used in this review. This memorandum is a collaborative review by the clinical and statistical review teams.

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

The following documents serve as the basis for this review:

- Original BLA 125764/0 submission
- FDA review of the docket information (FDA- 1997- N- 0010, Legacy Docket number 97N- 0497)
- FDA review of the COBLT Study (data available from the National Heart, Lung, and Blood Institute via its data-sharing portal at <https://biolincc.nhlbi.nih.gov/home/>)

The following FDA reviews were referenced in this clinical review. Links to these documents may be found in the [Appendix](#):

- Safety Review of Docket and Public Information
- Efficacy Review (Non-Oncology) – Docket and Public Information
- Efficacy Review (Oncology) – Docket and Public Information

5.3 Table of Studies/Clinical Trials

The Applicant submitted data from an observational, matched cohort study which examined outcomes after StemCyte facilitated UCBT compared to non-StemCyte UCBT (licensed and unlicensed). Patients underwent UCBT between January 2012 and December 2019.

5.4 Consultations

None

5.4.1 Advisory Committee Meeting

On September 22, 2011, the Cellular, Tissue, and Gene Therapies Advisory Committee discussed HEMACORD, which was the first-in-class HPC, Cord Blood BLA. No Advisory Committee Meeting was held for this BLA because there were no new concerns.

5.4.2 External Consults/Collaborations

None

5.5 Literature Reviewed

- a. Kharfan-Dabaja MA, Kumar A, Ayala E, et al. Standardizing Definitions of Hematopoietic Recovery, Graft Rejection, Graft Failure, Poor Graft Function, and Donor Chimerism in Allogeneic Hematopoietic Cell Transplantation: A Report on Behalf of the American Society for Transplantation and Cellular Therapy. *Transplant Cell Ther.* 2021 Aug;27(8):642-649.
- b. Ballen KK, Eliane Gluckman E, Broxmeyer HE, 2013, Umbilical cord blood transplantation: the first 25 years and beyond. *Blood.* 122(4): 491–498.
- c. American Academy of Pediatrics, 2017, Cord blood banking for potential future transplantation. *Pediatrics.* 2017 Nov;140(5).
- d. American Academy of Pediatrics, 2007, Cord blood banking for potential future transplantation. *Pediatrics* 119(1): 165-170.
- e. 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.
- f. 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.
- g. Yellowlees, P, C Greenfield, N McIntyre, 1980, Dimethyl sulfoxide-induced toxicity. *Lancet* 2:1004-1006.
- h. Petropoulou, AD and V Rocha. Risk factors and options to improve engraftment in unrelated cord blood transplantation, *Stem Cells Int.*, 2011;6:105-14.
- i. van Rood JJ, Stevens CE, Smits J, Carrier C, Carpenter C, Scaradavou A. Reexposure of cord blood to noninherited maternal HLA antigens improves transplant outcome in hematological malignancies. *Proc Natl Acad Sci U S A.* 2009 Nov 24;106(47):19952-7.
- j. Ruggeri A, Eapen M, Scaravadou A, Cairo MS, Bhatia M, Kurtzberg J, Wingard JR, Fasth A, Lo Nigro L, Ayas M, Purtill D, Boudjedir K, Chaves W, Walters MC, Wagner J, Gluckman E, Rocha V; for the Eurocord Registry, the Center for International Blood and Marrow Transplant Research, and the New York Blood Center. Umbilical Cord Blood Transplantation for Children with Thalassemia and Sickle Cell Disease. *Biol Blood Marrow Transplant.* 2011 Jan 28.
- k. Rafiee M, Abbasi M, Rafieemehr H, Mirzaeian A, Barzegar M, Amiri V, Shahsavan S, Mohammadi MH. A concise review on factors influencing the hematopoietic stem cell transplantation main outcomes. *Health Sci Rep.* 2021 May 7;4(2):e282.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

Not applicable. The Applicant did not conduct any prospective clinical trials to evaluate the efficacy or the safety of RegeneCyte. However, the Applicant did provide retrospectively collected data on the use of RegeneCyte from the Stem Cell Therapeutic Outcomes Database (SCTOD), provided by the Center for International Blood & Marrow Transplant Research (CIBMTR). The review of these data is provided in the Integrated Overview of Efficacy and Safety below.

7. INTEGRATED OVERVIEW OF EFFICACY

The efficacy of RegeneCyte is assessed through evidence of hematopoietic reconstitution in patients who received a suitable cord blood allograft (TNC $\geq 2.5 \times$

10^7 /kg of recipient weight, and $\geq 4/6$ degree of HLA match with patient). The assessment of efficacy is based primarily on historical review of the docket data, supplemented by current RegeneCyte data and considering publicly available data. Transplantation of RegeneCyte resulted in hematopoietic reconstitution, indicated by neutrophil, platelet, and erythrocyte recovery. Hematopoietic recovery varies with the degree of HLA matching and the TNC dose.

Published data and the docket data were reviewed independently and compared to data from RegeneCyte for this review. The RegeneCyte data included 54 patients who received a suitable allograft with 100-day follow-up data. The Applicant's data were obtained from the RegeneCyte internal database and from the Stem Cell Therapeutic Outcomes Database (SCTOD), provided by the Center for International Blood & Marrow Transplant Research (CIBMTR). The SCTOD is developed by the Health Resources and Services Administration of the US Department of Health and Human Services. As the contract holder, the CIBMTR is charged with collecting data on all allogeneic (related and unrelated) hematopoietic stem cell transplantations performed in the United States. All US transplant centers are required to report data to the CIBMTR; participation of non-US centers is voluntary.

Evaluable data for outcomes were not available for all patients and there were various amounts of missing data. Forty-four (44) patients had evaluable data for median TNC dose (from units $> 2.0 \times 10^7$) and 38 patients had evaluable data for platelet recovery $\geq 50,000/\mu\text{L}$ (excludes 16 patients (30%) with missing data). Eleven (11) patients (20%) died before platelet recovery; they were imputed with the longest recovery time in the analysis. Case report forms (CRF) for patients were not available, as data is collected incidentally in the course of clinical practice.

7.1 Indication

RegeneCyte is an allogeneic hematopoietic progenitor cell therapy proposed 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

Not applicable

7.1.2 Demographics and Baseline Characteristics

The timeframe for the data reported is January 2012 to December 2019. Of the 54 patients, 20 patients were transplanted with single units manufactured by the Applicant and 34 patients were recipients of double units where at least one unit was manufactured by the Applicant. Transplantation of the Applicant's product resulted in hematopoietic reconstitution, indicated by neutrophil and platelet recovery.

Demographics

Demographics of patients treated with an infusion of suitable allograft of RegeneCyte are shown in [Table 1](#). While comparisons between the Applicants' dataset and those of the

docket and COBLT study are limited by incomplete and missing docket and COBLT data, the demographics appear comparable with the exception of age. The RegeneCyte dataset had a median age of 37.5 years which is representative of a relatively larger enrollment of adult patients. Patients within the RegeneCyte dataset are categorized firstly as Hispanic, and then as all other races if non-Hispanic.

Table 1: Demographic Characteristics

Patient Characteristics	Docket (n = 1299)	RegeneCyte* (n = 54)
Median Age in Years (range)	7 (<1-66)	37.5 (0.1 – 70.3)
Age groups in years, n (%)		
< 2 years	393 (30%)	5 (9.3%)
2-17 years	786 (61%)	10 (18.5%)
>17 years	120 (9%)	39 (72.2%)
Sex, n (%)		
Male	524 (40%)	26 (48.1%)
Female	389 (30%)	28 (52.9%)
Unknown	386 (30%)	-
Race, n (%)		
White	573 (44%)	17 (31.5%)
Black or African-American	90 (7%)	9 (16.7%)
Hispanic	129 (10%)	21 (38.9%)
Asian	28 (2%)	4 (7.4%)
Other	14 (1%)	2 (3.7%)
Unknown/missing data	465 (36%)	1 (1.9%)
Ethnicity, n (%)		
Hispanic	-	21 (38.9%)
Non-Hispanic	-	32 (59.3%)
Unknown	-	1 (1.9%)
Diagnosis, n (%)		
Hematologic malignancies	862 (66%)	44 (81.5%)
Non-malignant disease	437 (34%)	10 (18.5%)
Inborn errors of metabolism	0 (0%)	1 (1.9%)
Immunodeficiency	93 (7%)	3 (5.6%)
Metabolic disorders	134 (10%)	-
Bone marrow failure	95 (7%)	2 (3.7%)
Hemoglobinopathy	8 (0.6%)	-
Other	107 (8%)	4 (7.4%)

*Data from patients who received a suitable allograft (TNC dose $\geq 2.5 \times 10^7$ cells/kg and HLA match $\geq 4/6$)

Reviewer Comment: Due to small number of patients and limitations of the Applicant's retrospective dataset, and associated missing data, no conclusions can be made about the correlation between demographics and clinical outcomes.

Product Characteristics

Major characteristics of the RegeneCyte units are summarized in [Table 2](#). Pre-cryopreservation total nucleated cell count is influenced by HLA mismatch and therefore also taken into consideration during this review. The median TNC dosage and HLA matching status of RegeneCyte appear comparable to those of the HPC, Cord Blood products that contributed to the docket information.

Table 2: RegeneCyte Unit Characteristics

	Docket (n = 1299)	RegeneCyte* (n = 54)
TNC dose/kg		
Median (x 10 ⁷ /kg)	6.4	5.8**
Range (x 10 ⁷ /kg)	2.5 – 73.8	2.2 – 34.4**
HLA Matching, n (%)		
6/6	143 (11%)	7 (13.0%)
5/6	524 (40%)	17 (31.5%)
4/6	583 (45%)	29 (53.7%)

* data from patients who received a suitable allograft (TNC dose $\geq 2.5 \times 10^7$ cells/kg and HLA match $\geq 4/6$)

** data for each outcome is only available in 44 patients

Reviewer Comment: Higher minimum TNC cell doses are recommended. However, unit selection can be complex because multiple characteristics must be considered. The minimum TNC cell dose thresholds for single unit grafts are influenced by additional factors such as HLA mismatch and malignant or nonmalignant cord blood transplantation indications. Units with higher HLA matching may have lower dose units contributing to the TNC range observed.

7.1.3 Patient Disposition

Not applicable

7.1.4 Analysis of Primary Endpoint(s)

The primary efficacy outcome was hematopoietic reconstitution as measured by neutrophil and platelet recovery. The Applicant did not include data regarding immunologic reconstitution. However, based on the Docket data and the publicly available data, HPC, Cord Blood has demonstrated the ability to reconstitute the immunologic system in patients transplanted for primary immunodeficiency, malignant and nonmalignant disorders ([Appendix](#)).

Neutrophil and Platelet Recovery

Time to and success of neutrophil and platelet recovery were assessed for patients who received suitable allografts. Neutrophil and platelet recovery were defined as per the American Society for Transplantation and Cellular Therapy definition (Kharfan-Dabaja MA, et al. 2021). Neutrophil recovery was defined as the first of three consecutive days with an absolute neutrophil count (ANC) greater than 500 cells per microliter (ANC > 500/ μ L), by Day 42, similar to that demonstrated in the pooled docket dataset and in the COBLT study. Platelet recovery by Day 100 was defined as the first of three consecutive days with a platelet count greater than 20,000 cells/ μ L in the absence of platelet transfusion for 7 consecutive days. The comparison of hematopoietic recovery in the COBLT, Docket, and RegeneCyte data are shown in [Table 3](#).

Table 3: Neutrophil and Platelet Recovery

Data Source	Docket (n = 1299)	COBLT Study (n = 324)	RegeneCyte (n = 54)
Neutrophil recovery at Day 42, % (95% CI)	77% (75%, 79%)	76% (71%, 81%)	91% (81%, 97%) ¹
Platelet recovery at Day 100 (20,000/ μ l), % (95% CI)	NA	57% (51%, 63%)	72% (58%, 83%) ¹
Platelet recovery at Day 100 (50,000/ μ l), % (95%CI)	45% (42%, 48%)	46% (39%, 51%)	73% (54%, 88%) ^{1,2}
Median time to Neutrophil Recovery	25 days	27 days	22 days
Median time to Platelet Recovery (20,000/ μ l)	NA	90 days	50 days ³
Median time to Platelet Recovery (50,000/ μ l)	122 days	113 days	64 days ³
Primary Graft Failure, %	16.4%	NA	9.3%

Source: Reviewer generated table comparing RegeneCyte dataset to publicly available Docket and COBLT study data.

Abbreviations: NA = Not Available, CI = Confidence Interval

¹ Cumulative incidence and 95% CI with arcsine square root transformation is presented.

² Thirty-four (34) patients had evaluable data for platelet recovery $\geq 50,000/uL$ (excludes 20 patients with missing data).

³ Eleven (11) patients (20%) died before platelet recovery. Their time to platelet recovery was imputed with the longest observed recovery time in the analysis.

Reviewer Comment: The cumulative incidence of neutrophil recovery (91%) and the median time to neutrophil recovery (22 days), associated with StemCyte's HPC, Cord Blood are comparable to these outcomes for HPC, Cord Blood products that contributed to the docket data and the COBLT study. The incidence of primary graft failure of the Applicant's product (9.3%) also appears comparable to that of the HPC, Cord Blood products that contributed to the docket data. Note that comparisons are limited by incomplete and missing data from retrospective observational data (including insufficient information about the nature and severity of the diseases that were the primary indications for transplantation and the conditioning regimens) and demographic differences between the Applicant's dataset and the docket and COBLT study.

Neutrophil Recovery, HLA matching and TNC dose

Analysis of docket data has indicated that the TNC dose and degree of HLA matching are inversely associated with the time to neutrophil recovery ([Appendix](#)).

7.1.5 Analysis of Secondary Endpoint(s)

None

7.1.6 Other Endpoints

None

7.1.7 Persistence of Efficacy

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

7.1.9 Product-Product Interactions

The BLA submission does not include data regarding the effect of concomitant medications, devices, or therapies on the efficacy of RegeneCyte.

7.1.10 Additional Efficacy Issues/Analyses

None

7.1.11 Efficacy Conclusions

Efficacy of HBC, Cord Blood for the proposed indication has been previously established through review of docket data and the publicly available data, including the COBLT Study. Despite the limitations of RegeneCyte data related to sample size and lack of standardization of the data collection, the RegeneCyte data can still be used to provide supportive evidence of effectiveness. Compared to the FDA docket and publicly available cord blood data, RegeneCyte demonstrated similar efficacy. Neutrophil recovery by day 42 occurred in 91% of patients and platelet recovery by day 100 occurred in 72%.

The Applicant's data do not include information to evaluate immunologic reconstitution following RegeneCyte transplantation. However, based on the docket and publicly 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 ([Appendix](#)).

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Safety of HPC, Cord Blood, has previously been established. The safety analysis of this product is based on review of RegeneCyte data from 54 patients, and comparison to the Docket and publicly available data.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The source of RegeneCyte safety data is an observational, matched cohort study examining transplant patients who received RegeneCyte. These data are compared to patients who received non-RegeneCyte HPC, Cord Blood. Transplant data was collected from the SCTOD, provided by the CIBMTR.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Please see [Table 1](#) for the demographic characteristics, and [Table 2](#) for the dose exposure and cord blood unit characteristics for the population of patients in the RegeneCyte dataset who received a suitable allograft (Section 7.1.2 of this review).

8.2.3 Categorization of Adverse Events

The safety review focuses on the adverse events that are commonly reported in the literature as primarily transplantation-related and include: 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](#)).

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

Not applicable

8.4 Safety Results

8.4.1 Deaths

Early mortality is defined as death within 100 days post-transplantation (Day 100 mortality). During this initial 100 days, the risk is highest for critical side effects and acute graft versus host disease as the stem cells have not yet engrafted and instigated making new blood cells. In the RegeneCyte dataset, 13% of patients who received a suitable allograft experienced early mortality, compared to 25% of patients that comprised the Docket dataset.

Table 4: Comparison of RegeneCyte HPC, Cord Blood Mortality Data with Docket Data

Deaths	Docket (n = 1299)	RegeneCyte (n = 54)
Total Mortality, n (%)	635 (48.9%)	28 (51.9%)
Early Mortality (Day 100), n (%)	328 (25.3%)	7 (13%)

Reviewer Comment: The mortality rate observed in the RegeneCyte data is based on a relatively small subset of patients who received RegeneCyte. Overall, the death rate of RegeneCyte appears comparable to that of HPC, Cord Blood products that contributed to the docket data.

[Table 5](#) compares the demographic characteristics for patients who experienced early mortality in the RegeneCyte dataset as compared to the Docket dataset. RegeneCyte dataset is insufficient to draw conclusions about the interaction between demographics and early mortality due to the small number of patients with early mortality. The limited data categorizing early mortality outcomes by demographic characteristics appear to be comparable to the experience in the Docket data.

Table 5: Early Mortality (death < 100 days) with Demographic Characteristics

Patient Characteristics	Docket (n = 328)	RegeneCyte (n = 7)
Median Age (range) in years	-	35.9 (4.8 – 70.3)
Age groups in years, %		
<2 years	22.3%	-
2-17 years	27.4%	28.6%
>17 years	48.6%	71.4%
Sex, %		
Male	18.1%	57.1%
Female	27.0%	42.9%
Unknown	54%	
Ethnicity/Race, %*		
White	22.3%	28.6%
Black or African-American	28.9%	14.3%
Hispanic	18.9%	42.9%
Asian	19.4%	-
Other	31.3%	14.3%
Diagnosis, n (%)		
Hematologic Malignancies	46.5%	100%
Non-malignant disease	-	-
Inborn Errors of Metabolism	32.0%	-
Immunodeficiency	17.7%	-
Metabolic Disorders	-	-
Bone Marrow Failure	23.4%	-
Hemoglobinopathy	-	-
Other	-	-

*Patients within the CIBMTR dataset are categorized firstly as Hispanic, and then as all other races if non-Hispanic

[Table 6](#) shows the causes of death after transplantation. For RegeneCyte patients who received a suitable allograft, death prior to Day 100 post-transplantation was most commonly caused by organ failure (3 of 54; 5.4%) and infection (2 of 54; 3.7%) which was consistent with available data from the docket dataset. The included observational data reported to the Center for International Blood and Marrow Transplant Research did not provide any discussion of the cause of organ failure in the 3 patients who died of organ failure within the first 100 days. The observational data did not include any adverse events of engraftment syndrome, malignancies of donor origin, or transmission of serious infection which may have contributed to organ failure. There were no reported deaths caused by graft failure in the limited RegeneCyte dataset.

Table 6: Causes of Death after Transplantation in RegeneCyte and Docket Datasets

Causes of Death	Docket (n = 1289)		RegeneCyte (n = 54)	
	Total Deaths n = 631 (49%)	Deaths ≤ Day 100 n = 328 (25.3%)	Total Deaths n = 28 (51.9%)	Deaths ≤ Day 100 n = 7 (13.0%)
Infection, n (%)	170 (13%)	101 (8%)	4 (7.4%)	2 (3.7%)
Primary disease, n (%)	168 (13%)	39 (3%)	12 (22.2%)	1 (1.9%)
Organ failure, n (%)	115 (8.9%)	84 (7%)	6 (11.1%)	3 (5.4%)
GVHD, n (%)	72 (6%)	39 (3%)	2 (3.7%)	-
Unknown, n (%)	54 (4%)	32 (2%)	-	-
Graft failure, n (%)	48 (4%)	33 (3%)	0	0
Second malignancy, n (%)	4 (< 1%)	0	1 (1.9%)	-
Prior malignancy, n (%)	-	-	-	-
Hemorrhage, n (%)	-	-	-	-
Pulmonary toxicity, n (%)	-	-	1 (1.9%)	1 (1.9%)
Other*, n (%)	0	0	2 (3.7%)	-

* Note that further interpretation of this category was not possible due to the limitations of the data provided by CIBMTR.

Reviewer Comment: The high overall mortality rate is likely due to the high-risk patient population. Organ toxicity associated with the intensive treatment administered to patients before UCBT is another leading cause of mortality in patients.

8.4.2 Nonfatal Serious and Non-serious Adverse Events

Primary Graft Failure

Primary graft failure is defined as failure to achieve ANC > 500/μL by Day 42. One patient who did not have evaluable data for neutrophil recovery by Day 42, due to death prior to Day 42, is not included in the analysis as primary graft failure. Immunological rejection is the primary cause of graft failure and may be fatal. Primary graft failure was reported in 9.3% of recipients (5 of 54 patients), within the population of patients who received RegeneCyte and had evaluable hematopoietic reconstitution data. This is comparable to the 16% incidence of primary graft failure in the docket data.

Infusion Reactions

Infusion reactions are defined as AEs occurring within 24 hours after transplantation. The causes of infusion reactions may include reactions to hemolyzed HPC, Cord Blood, allergic or anaphylactic reactions to any component of HPC, Cord Blood, or bacterial contamination. The data from the COBLT study, shown in [Table 7](#), included exposure to 442 infusions of HPC, Cord Blood (from multiple cord banks) in patients treated with TNC $\geq 2.5 \times 10^7/\text{kg}$ in a single-arm trial. The population, which was 60% male and had a median age of 5 years (range 0.05 – 68 years), included patients treated for hematologic malignancies, inherited metabolic disorders, primary immunodeficiencies, and bone marrow failure. Preparative regimens and graft-versus-host disease prophylaxis were not standardized. The most common infusion reactions were hypertension, vomiting, nausea, and bradycardia. Hypertension and Grade 3-4 infusion-related reactions

occurred more frequently in patients receiving volumes greater than 150 milliliters and in pediatric patients. The rate of serious adverse cardiopulmonary reactions was 0.8%.

Information on infusion reactions was available from 54 patients who received suitable allografts with the Applicant's HPC, Cord Blood. [Table 7](#) shows the incidence of infusion reactions with the Applicant's product (7.4%) as compared to the COBLT data (65.4%). Comparisons between the Applicant's dataset and those of the COBLT study are limited by the total number of patients included in RegeneCyte data. The large difference in adverse infusion reactions (65.4% vs 7.4%) could represent a true difference between the products; however, differences in the percentage of infusion reactions may reflect contribution of other factors such as variations in demographic characteristics such as age and underlying comorbidities. Comparison of the two values is further limited by the small sample size and differences in data collection. Preparative regimens and GVHD prophylaxis were not standardized. The reactions were not graded for severity. The most commonly reported infusion reaction with the Applicant's product, was hypertension (3.7%), which was lower compared to the COBLT database (48%).

Table 7: Incidence of Infusion Reactions

Infusion Reactions	COBLT Infusions with a TNC Dose $\geq 2.5 \times 10^7/\text{kg}$ n = 442	RegeneCyte n = 54
Total	65.4%	4 (7.4%)
Hypertension	48.0%	2 (3.7%)
Nausea	12.7%	1 (1.9%)
Vomiting	14.5%	1 (1.9%)
Hypotension	2.5%	-
Hypoxia	2%	-
Headache	0	-
Tachycardia	4.5%	-
Shortness of breath	0.9%	-
Chest Pain	-	1 (1.9%)
Fever	5.2%	-
Chills	0.9%	-
Hives	-	-
Bradycardia	10.4%	-
Other	-	-

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

Graft-versus-Host Disease (GVHD)

GVHD is a common complication following unrelated cord blood transplantation. Immune T-cells in donor cord blood identify the recipient as foreign and attack the host's cells.

Acute GVHD is defined as occurring within the first 100 days post transplantation and affects primarily liver, skin, mucosa and the gastrointestinal tract. The frequency of acute GVHD appears similar in the RegeneCyte dataset and the docket dataset ([Table 8](#)). Categorizing acute GVHD by grade, there appear to be similar proportions of patients in each subset between the two datasets.

Table 8: Incidence of Acute GVHD (Grade 1-4)

Occurrence of Acute GVHD	Docket (n = 1182)	RegeneCyte (n = 54)
No*	369 (31%)	17 (31.5%)
Unknown	-	6 (11.1%)
Yes	813 (69%)	31 (57.4%)
Grade 1	315 (27%)	6 (19.4%)
Grade 2	276 (23%)	15 (48.4%)
Grade 3	149 (13%)	8 (25.8%)
Grade 4	73 (6%)	2 (6.5%)

*Competing risk of death is categorized as 'No' for the occurrence of acute GVHD.

Chronic GVHD occurs after 100 days post-transplantation. Incidence of chronic GVHD is shown in [Table 9](#). Extensive chronic GVHD was reported in 9 (16.7%) patients.

Table 9: Incidence of Chronic GVHD after Infusion with RegeneCyte

Occurrence of Chronic GVHD	RegeneCyte
Yes	11 (20.4%)
- Limited	2 (3.7%)
- Extensive	9 (16.7%)
No	20 (37.0%)
Not Indicated	23 (42.6%)

Engraftment Syndrome

Engraftment syndrome is an inflammatory condition which manifests as unexplained fever and rash during neutrophil recovery after hematopoietic stem cell transplantation. Patients with engraftment syndrome may also have unexplained weight gain, hypoxemia, and non-cardiogenic pulmonary edema. The Applicant did not report any cases of engraftment syndrome. Based on the docket data and on publicly available data ([Appendix](#)), engraftment syndrome occurred in 15% of the 364 patients in the COBLT study. In literature reports, the incidence of engraftment syndrome varies from 30% to 78%. Risk of engraftment syndrome was not included in the Docket dataset.

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

There are no reports of possible transmission of malignancy, serious infection, or genetic disease from the donor material in the RegeneCyte dataset. Data from published literature and from observational registries, institutional databases, and cord blood bank reviews reported to the docket for HPC, Cord Blood (from multiple cord blood banks) are not sufficient to support reliable estimates of the incidence of these events.

Summary of Major Adverse Events Associated with RegeneCyte

The safety review of this BLA focuses on transplantation-related adverse events (AEs), including early mortality (prior to Day 100), infusion reactions, graft versus host disease (GVHD), and graft failure summarized in [Table 10](#).

Table 10: Summary of Major Adverse Events Associated with RegeneCyte

Major Adverse Event	Docket (n = 1299) or COBLT (n = 324)	RegeneCyte (n = 54)
Early Mortality (Day 100), %	25% (Docket)	13.0%
Primary Graft Failure, %	16% (Docket)	9.3%*
Infusion Reactions, %	65% (COBLT)	7.4%
Acute Graft Versus Host Disease (aGVHD), %	69% (Docket)	46.3%
Chronic Graft Versus Host Disease (cGVHD), %	-	20.4%

*Primary graft failure is defined as patients who did not achieve neutrophil recovery by day 42 (ANC > 500/ μ L). 1 patient died before measurement of neutrophil recovery by day 42. Competing risk due to death is classified as primary graft failure.

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

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

8.5.2 Time Dependency for Adverse Events

Please see section 8.4 for analyses of total death and early mortality at Day 100 post-transplantation.

8.5.3 Product-Demographic Interactions

Please see FDA review of docket and public information ([Appendix](#)) for analyses of product-demographic interactions regarding safety (graft failure) and efficacy (neutrophil recovery) by age, sex, 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 FDA review of Docket and public information ([Appendix](#)) for information on overdose of HPC, Cord Blood products. The Applicant did not provide information on overdose of their product. The product contains 10% dimethyl sulfoxide (DMSO). The maximum tolerated dose of DMSO has not been established, but it is customary not to exceed a daily DMSO dose of 1 gm/kg when given intravenously, which is the DMSO content of (b) (4) ml/kg of RegeneCyte. While administration of this volume of RegeneCyte is improbable, toxic overdose of DMSO has been reported in a patient undergoing autologous HPC – bone marrow transplantation (Yellowlees, Greenfield, et al. 1980). However, no report of a DMSO overdose related to HPC, Cord Blood transplantation was found during review of the published literature.

The BLA submission does not include data regarding the abuse potential, withdrawal, and rebound of the Applicant's product.

8.5.8 Immunogenicity (Safety)

RegeneCyte 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 the preparative regimens are major safety concerns. Please see Sections 8.4.1 and 8.4.2 of this review for details.

8.5.9 Person-to-Person Transmission, Shedding

Transplantation of RegeneCyte may result in the development of malignancies of donor origin, or transmission of serious infection or rare genetic diseases ([Appendix](#)). No such cases were reported in this BLA.

8.6 Safety Conclusions

Based primarily on the Docket data and supplemented by the RegeneCyte data and publicly available data, the risks associated with RegeneCyte HPC, Cord Blood transplantation can be serious and potentially fatal. The adverse events include early death, infusion reactions, graft versus host disease (GVHD), and graft failure. The Applicant did not report any cases of engraftment syndrome, malignancies of donor origin, or transmission of serious infection or rare genetic disease..

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

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

There are no data with RegeneCyte use in pregnant women to inform a product-associated risk. Animal reproduction studies have not been conducted with this product.

9.1.2 Use During Lactation

This BLA does not include information regarding the safety of using RegeneCyte during lactation including the presence of RegeneCyte in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for this product and any potential adverse effects on the breastfed infant from RegeneCyte or from the underlying maternal condition.

9.1.3 Pediatric Use and PREA Considerations

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

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

9.1.4 Immunocompromised Patients

RegeneCyte 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 RegeneCyte from multiple cord blood banks included six patients 65 years or older. There were insufficient numbers of patients ≥ 65 years of age to determine whether geriatric patients respond differently from younger patients.

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

None

10. CONCLUSIONS

Compared to the docket and publicly available cord blood data, RegeneCyte demonstrated similar efficacy and safety to available cord blood products. Neutrophil and platelet recovery and the median time to neutrophil and platelet recovery, associated with RegeneCyte are comparable to these outcomes for HPC, Cord Blood products that contributed to the docket data and the COBLT study. The adverse events associated with RegeneCyte and other HPC, Cord Blood transplantation products include early death, infusion reactions, graft versus host disease (GVHD), and graft failure which are serious and potentially fatal.

Based on the previous determination of safety and effectiveness of HPC, Cord Blood based primarily on the Docket data, and publicly available data and supplemented by the

Applicant's data, we conclude that RegeneCyte is capable of hematopoietic and immunologic reconstitution in conjunction with a preparative regimen. RegeneCyte is a safe and effective source of hematopoietic progenitor cells for transplantation to treat diseases affecting the hematopoietic system.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

[Table 11](#) documents the risk-benefit considerations for this BLA.

Table 11: Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> The disorders this product is proposed to treat are broadly defined as “disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.” Hematopoietic progenitor cell transplantation (HSCT) is most commonly performed as a treatment for hematologic malignancies. Other types of disorders that may be treated with HSCT are metabolic disorders, bone marrow failure, hemoglobinopathy, immunodeficiency, and autoimmune disorders. Many of these disorders are serious and have limited treatment options. HSCT procedures require potentially toxic preparative regimens. 	<ul style="list-style-type: none"> Hematological malignancies and bone marrow failure are serious and life-threatening diseases. Metabolic disorders, hemoglobinopathies, immunodeficiencies, and autoimmune diseases are serious and can be life-threatening if severe and/or late stage More treatment options are needed for disorders affecting the hematopoietic system Reconstitution of the hematopoietic system is essential after ablative treatments of the hematopoietic system.
Unmet Medical Need	<ul style="list-style-type: none"> Alternatives to HSCT vary by disorder but could include chemotherapy, immunotherapy, replacement therapy, and targeted biologic agents, which has significant risks, such as increasing a patient’s susceptibility to infection. For diseases warranting treatment with HSCT, an HLA-matched donor may not be available. Those of non-white or mixed race may be especially difficult to match³ and have the greatest need for alternatives sources of stem cells. Cord blood is used for HSCT when an HLA-matched bone marrow or peripheral blood donor is not available, because cord blood cells are immunologically naïve and therefore more tolerant of HLA mismatch 	<ul style="list-style-type: none"> Approved therapies exist for many of the disease of the hematopoietic system that might be treated with this product, although efficacy of many of these therapies are limited, driving the need for treatment via HSCT. There is an inadequate supply of stem cell donors for all patients warranting allogeneic HSCT to be able to receive an HLA-matched bone marrow or peripheral blood stem cell donation. RegeneCyte provides another source of HPC, Cord Blood for allogeneic transplant.
Clinical Benefit	<ul style="list-style-type: none"> A single-arm prospective study (COBLT), 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 Applicant’s database demonstrated comparable results for hematopoietic reconstitution as compared with the COBLT and Docket data. The clinical benefit of RegeneCyte has not been demonstrated through formal hypothesis testing. 	<ul style="list-style-type: none"> Cord blood is an effective source of stem cells for hematopoietic reconstitution, providing potentially curative treatment for serious or life-threatening disorders affecting the hematopoietic system where other therapies have not been effective and other sources of stem cells for transplant and not available. Retrospective data provide evidence to support the comparability of the Applicant’s cord blood to the class of HPC, Cord Blood The Applicant’s data do not include information about immunologic reconstitution. However, based on the analyses of the docket data and publicly available data, HPC, Cord Blood has demonstrated the ability of to reconstitute the immunologic system for patients

³ [Why Ethnicity Matters When Donating Bone Marrow | Be The Match](#) (accessed May 4, 2024)

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
		transplanted for primary immunodeficiency as well as other for other malignant and non-malignant disorders.
Risk	<ul style="list-style-type: none"> • Risks have been characterized through the Docket and COBLT data and reflecting the HPC, Cord Blood class, due to the large sample size • All-cause mortality rate was 30% at 100 days post-transplant as result of infection, primary disease, pulmonary causes, multi-organ failure, and GVHD • Acute GVHD occurred in 69%, and may have been beneficial for a subset of patients with hematologic malignancy (Graft versus tumor effect) • Infusion reactions in occurred in 65% (COBLT), including hypertension, nausea, vomiting, sinus bradycardia, fever, sinus tachycardia, allergy, hypotension, hemoglobinuria, and hypoxia. RegeneCyte data from a limited number of patients suggests a lower rate. • Primary Graft failure occurred in 16% 	<ul style="list-style-type: none"> • Risks of HPC, Cord Blood transplantation and the myeloablative preparative regimen can be serious and life-threatening. • If HSCT is warranted, other stem cell sources such as autologous or match bone marrow or peripheral cells should be considered. • The profile of adverse events associated with RegeneCyte is comparable to that observed in other HPC, Cord Blood products contributing to the docket set.
Risk Management	<ul style="list-style-type: none"> • There are many serious risks of HSCT and these adverse reactions can be acute, sub-acute, or delayed in onset. • Infusion reactions are a serious acute adverse reactions • Serious subacute or delayed adverse reactions include engraftment syndrome, GVHD, graft failure, malignancies of donor origin, and transmission of serious infections or genetic diseases. 	<ul style="list-style-type: none"> • The serious risks of HSCT are already well-known to prescribers and mitigating measures incorporated into standard procedures in transplant centers. • Early, potentially fatal risks of infusion reaction, GVHD, engraftment syndrome, and graft failure are appropriate for a boxed warning • . • No safety issues were identified to warrant PMC or PMR. Routine post marketing pharmacovigilance is considered sufficient for risk management

11.2 Risk-Benefit Summary and Assessment

Allogeneic hematopoietic progenitor cell transplantation is an important and potentially curative treatment option for a wide variety of malignant and nonmalignant diseases. Umbilical cord blood serves as an alternate source of pluripotent hematopoietic stem cells required for allogeneic HCT. The FDA Guidance for Industry: *Biologics License Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System* (2014) provides manufacturing and licensing guidance for cord blood collection and preparation. Since initial approval of the first cord blood product manufactured by New York Blood Center in 2011, seven additional cord blood products have been approved and the safety of HPC, Cord Blood is well-characterized. Therefore, even with limited clinical data specific to RegeneCyte, I recommend approval based FDA's previous conclusion of safety and efficacy of HPC, Cord Blood, and overall similar safety and efficacy data for RegeneCyte. RegeneCyte has demonstrated a favorable overall risk-benefit profile through its ability to reconstitute the immunologic system in patients transplanted for primary immunodeficiency, malignant and nonmalignant disorders (Section 12, [Appendix](#)).

Transplantation of RegeneCyte resulted in hematopoietic reconstitution, indicated by percentage of patients achieving Day 42 neutrophil and Day 100 platelet recovery, which were 91% and 72% respectively. Potential risks associated with RegeneCyte transplantation, including primary graft failure, graft versus host disease and infusion reactions, which can be appropriately addressed in the US Prescribing Information and the proposed pharmacovigilance plan.

Transplantation for hematopoietic and immunologic reconstitution is a potentially life-saving treatment for certain diseases such as malignancies, inborn errors of metabolism, and immunodeficiencies affecting the hematopoietic system. The benefit-risk assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells. Risks include early death, infusion reactions, GVHD, engraftment syndrome, and graft failure.

11.3 Discussion of Regulatory Options

The regulatory options include (1) standard approval; or (2) Complete Response (CR).

11.4 Recommendations on Regulatory Actions

Based on overall benefit-risk consideration of the docket and published data referenced in this application, and supplemented by the RegeneCyte data, the FDA clinical and statistical reviewers recommend approval of RegeneCyte 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

Labeling for HPC, Cord blood is product class labeling. Therefore, the labeling of RegeneCyte will follow the labeling of previously approved HPC, Cord blood products.

Reviewer Comment: Clinical and statistical reviewers had comments and revised Applicant's submitted prescribing information to ensure consistency with product class labeling.

11.6 Recommendations on Postmarketing Actions

There are no safety issues related to RegeneCyte that trigger a Risk Evaluation and Mitigation Strategy (REMS) or warrant postmarketing requirement (PMR) or postmarketing commitment (PMC) studies. The Applicant will perform routine pharmacovigilance, which includes AE reporting in accordance with 21 CFR 600.80: 15-day expedited reporting for serious and unexpected adverse events and submission of periodic safety reports (quarterly for 3 years after licensure, annual thereafter). In response to an information request dated July 5, 2022, the Applicant also confirmed that they will perform the following activities that consistent with other members of this product class:

- a. Implement a safety outcome 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 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 a 15-day "alert report" for each serious infusion reaction associated with administration of HPC, cord blood.

These measures will be adequate to monitor postmarketing safety for the Applicant's HPC, cord blood.

12. APPENDIX

This Appendix provides the references/links to FDA's prior review of the docket information (FDA- 1997- N- 0010, Legacy Docket number 97N- 0497) and the COBLT Study.

Reviews available as supporting documents in the folder [Approval History, Letters, Reviews and Related Documents - Hemacord](https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/hemacord-hpc-cord-blood) at <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/hemacord-hpc-cord-blood>

- 12.1 Safety Review: Hematopoietic Progenitor Cells-Cord Blood; Primary Reviewer: Donna Przepiorka, M.D., Ph.D., October 28, 2011
- 12.2 Clinical Efficacy Review, Nonmalignant Indications: Hematopoietic Progenitor Cells-Cord Blood; Primary Reviewer: John E. Hyde, Ph.D., M.D., November 3, 2011

Review available as supporting documents in the folder [Supporting Documents older than three years – Hemacord](http://wayback.archive-it.org/7993/20170723025414/https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM282140.pdf) at <http://wayback.archive-it.org/7993/20170723025414/https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM282140.pdf>

- 12.3 Malignant Efficacy Review, Malignant Indications: Hematopoietic Progenitor Cells-Cord Blood; Primary Reviewer: Maura O’Leary, M.D., November 9, 2011