**Summary Basis for Regulatory Action**

| | |
|---|---|
| **Date:** | November 20, 2024 |
| **From:** | Saravanan Karumbayaram, M Pharm, PhD<br>Review Committee Chair,<br>CBER/OTP/OCTHT/DCT1/CTB1 |
| **BLA STN:** | BLA 125764/0 |
| **Applicant:** | StemCyte, Inc. |
| **Submission Receipt Date:** | Original Submission: January 7, 2022<br>Resubmission: November 29, 2023 |
| Non-PDUFA **Action Due Date:** | May 10, 2024 |
| **Proper Name:** | HPC, Cord Blood |
| **Proprietary Name:** | REGENECYTE |
| **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. |

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

_____

**Director, Office of Clinical Evaluation**

_____

**Director, Office of Compliance and Biologics Quality**

| Discipline Reviews | Reviewer / Consultant - Office/Division |
|---|---|
| **CMC**<br>• CMC Product (OTP/OCTHT)<br><br><br><br><br>• Facilities review (OCBQ/DMPQ)<br>• Establishment Inspection Report (OCBQ/DMPQ and Product Office)<br>• QC, Test Methods, Product Quality (OCBQ/DBSQC) | Saravanan Karumbayaram, M Pharm, PhD, CBER/OTP/OCTHT<br>Mercy Quagraine, PhD, CBER/OTP/OCTHT<br>Fatima Abbasi, MS, MPH, CBER/OTP/OCTHT<br>Hanh Khuu, MD, CBER/OTP/OCTHT<br><br>Xiuju (Sue) Lu, PhD, CBER/OCBQ/DMPQ<br><br>Prajakta Varadkar, PhD, CBER/OCBQ/DMPQ<br><br>CDR Donald Ertel, MS, MT(ASCP), CBER/OCBQ/DMPQ<br>Maryna Eichelberger, PhD, CBER/OCBQ/DBSQC<br>Carolyn Renshaw, CBER/OCBQ/DMPQ |
| **Clinical**<br>• Clinical (Product Office) | Prateek Shukla, MD, CBER/OTP/OCE<br>Leah Crisafi, MD, CBER/OTP/OCE<br>Vaishali Popat, MD,MPH, CBER/OTP/OCE |
| **Statistical**<br>• Clinical data (OBPV/DB)<br>• Non-clinical data | Thomas Zhou, PhD, CBER/OBPV/DB<br>Boguang Zhen, PhD, CBER/OBPV/DB |
| **Labeling**<br>• Promotional (OCBQ/APLB)<br><br>• USPI Review | Michael Brony, PhD, CBER/OCBQ/DCM<br>Lisa Stockbridge, PhD, CBER/OCBQ/DCM/APLB<br>Afsah Amin, MD, MPH CBER/OTP/OCE |

## Table of Contents



## 1. Introduction

StemCyte, Inc submitted a Biologics License Application (BLA) 125764 to seek licensure of HPC (Hematopoietic Progenitor Cell), Cord Blood (HPC, Cord Blood). The proprietary name of the product is REGENECYTE. REGENECYTE is an allogeneic hematopoietic progenitor cell therapy indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment. The benefit-risk assessment for an individual patient depends on the patient

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

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

## 2. Background

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

### Regulatory History

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

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

On January 7, 2022, StemCyte, Inc. submitted a BLA to request licensure of REGENECYTE. The applicant followed FDA guidance recommendations and cited dockets FDA-1997-N-0010 (Legacy Docket number 97N-0497) and FDA-2006-D-0157 (Legacy Docket number 06D-0514) for the efficacy and safety data to support this application. The BLA also includes the applicant's safety outcomes dataset to support the safety of the product.

FDA issued a Complete Response Letter (CRL) 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 CRL comments in a resubmission on November 9, 2023, and subsequently addressed all CRL items during the review.

## 3. Chemistry, Manufacturing, and Controls (CMC)

### a. Product Quality

#### Product Description

REGENECYTE is the proprietary name for the HPC, Cord Blood, drug product manufactured by StemCyte. Each lot of REGENECYTE is manufactured from a single cord blood unit (CBU) reduced of volume and red blood cells (red cell reduced (RCR)). The final product contains 25ml of nucleated cells cryopreserved in 10% DMSO and 1% Dextran 40 solution, divided into a two compartment cryobag that holds 80% and 20% of the volume. Each lot contains a minimum of $90 \times 10^7$ total nucleated cells with a minimum of $1.25 \times 10^6$ viable CD34+ cells. HPC, Cord Blood should be thawed and washed at the clinical site per the instruction for use and administered to the patients.

#### Summary of the Manufacturing Process

Mothers who consent to donate their newborn's cord blood for public banking are screened and tested for communicable infectious diseases per 21 CFR 1271 Subpart C. CBUs are collected in (b) (4) cord blood collection bag from qualified facilities in (b) (4) and transported to the StemCyte Manufacturing facility in Baldwin Park, CA, in validated shipping containers that maintain temperature between (b) (4) (b) (4) CBUs are evaluated upon receipt to determine if minimum requirements (b) (4) are met prior to processing. CBUs are also sampled to test pre-processing (b) (4) (specification: (b) (4) (b) (4) Each CBU that passed the pre-processing test is assigned a subsequent International Society of Blood Transfusion (ISBT) number for global traceability. The manufacture of REGENECYTE is done in a (b) (4) (b) (4) Then (b) (4) sample is aliquoted for (b) (4) assay, post-TNC count, (b) (4) viability, and CD34+ cell count. The rest of the HPC, Cord Blood is cryopreserved in 10% DMSO and 1% Dextran 40. There are no reagents or excipients from human or animal sources used in the manufacturing of HPC, Cord Blood.

#### Summary of Manufacturing Process Controls

Donor testing is performed on birth mother blood specimens collected within 7 days of the infant's delivery. The CBU should be processed within 48 hours of collection. Hemoglobin analysis and ABO/Rh typing are performed on pre-processing cord blood samples. The CBU shipping temperature should be between (b) (4) The CBUs have specific (b) (4) (b) (4) as a pre-processing requirement. Since the product is manufactured in a (b) (4) system, within a (b) (4) period of time (b) (4) in-process testing during the (b) (4) process is not feasible. Lot release testing is performed in an aliquot of REGENECYTE, and it should meet the

specifications as shown in Table 1. Confirmatory HLA typing is performed on the cryobag segment at the time of release for transplantation.

**Specification for HPC, Cord Blood Drug Product**

**Table 1: HPC, Cord Blood Specifications**

| Parameter | Specification | Sampling and Method |
|---|---|---|
| TNC count | ≥ 90 x$10^7$ | (b) (4) |
| Viable TNC | ≥ 85% | (b) (4) |
| Viable total CD34+ cells | ≥ 1.25 x$10^6$ | (b) (4) |
| Microbial testing (Sterility) | No detectable microbial growth | (b) (4) |
| (b) (4) assay (b) (4) | (b) (4) (b) (4) | (b) (4) |
| Donor screening and infectious disease testing | Donor meets criteria defined in CFR 1271, Subpart C.<br>All infectious disease markers are tested non-reactive/negative.<br>CMV results are recorded. | Maternal history questionnaire<br>Maternal blood obtained within 7 days of cord blood collection / FDA licensed, cleared, or approved test kits.<br>All donor screening and testing results reviewed, and donor eligibility determined by Medical Director |
| Human leukocyte antigen (HLA) typing | Report | (b) (4) |
| Confirmatory HLA typing | Confirms initial typing | (b) (4) |
| ABO/Rh type | Report | (b) (4) |

| | | |
|---|---|---|
| Hemoglobin Testing | No homozygous or double heterozygous for hemoglobinopathy | (b) (4) |

**Acronym key**: HLA- Human Leukocyte Antigen; Rh- Rhesus Factor; TNC-Total Nuclear Count; CD-Cluster of Differentiation; (b) (4) USP – United States Pharmacopeia; CLIA - Clinical Laboratory Improvement Amendments.

**Process Validation**

During the original BLA review period, the Applicant made several changes in the testing procedures used to evaluate the quality of the HPC, Cord Blood. In addition, they did not provide a comprehensive protocol for the entire process validation that demonstrated CBU collection, shipment from collection site to manufacturing facility, pre-process testing, (b) (4) processing to generate HPC, Cord Blood, post process testing, cryopreservation, and thawing and washing of HPC, Cord Blood. The process validation data were not derived from consecutively collected samples and they were not validated using the updated testing methods. In the resubmission, the Applicant provided the protocol and report for the updated process validation (PV) beginning with CBU collection through thawing and washing of the product. The Applicant collected (b) (4) CBUs for process validation, (b) (4) of which passed the pre-processing (b) (4) and (b) (4) of the (b) (4) CBUs passed the pre-processing (b) (4) Further, the Applicant performed the entire manufacturing process, to include thaw and wash, on (b) (4) of the (b) (4) CBUs to show that they were able to consistently manufacture the HPC, Cord Blood product meeting pre-determined specifications.

**Drug Product Stability**

The Applicant describes a stability program to assess the stability of the cryopreserved HPC, Cord Blood in support of the storage conditions and to advance expiration dating. (b) (4) randomly selected oldest lots of HPC, Cord Blood were used to determine product stability. The parameters used to determine stability are TNC recovery, viable TNC count, viable CD34+ cell count, (b) (4) sterility and integrity of the cryobag. Based on the stability study results, the expiration of the HPC, Cord Blood is established at 12 years. The Applicant has a stability program in place to extend the expiry date annually, if appropriate.

**Manufacturing Risks, Potential Safety Concerns, and Management**

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

To address the communicable disease risks, medical records are reviewed for high-risk exclusion, and mothers of the newborn donors are screened and tested for

communicable diseases according to 21 CFR 1271 regulations. Cord blood collection is performed at qualified sites and performed according to instructions and in designated areas or delivery suites by staff or healthcare providers trained to use aseptic technique, and to collect one CBU at a time.

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

To address contamination risks, collection and processing methods are functionally (b) (4) and have been validated to ensure aseptic processing. The cryoprotectant is added to the processed HPC, Cord Blood using aseptic technique. Post-processing samples are tested for microbial contamination and must be negative. In addition, the validated thaw and wash procedure recommends following aseptic techniques during thawing and using a secondary sterile Ziploc™ bag while thawing the product to prevent any direct contact of the primary bag with the water bath. The Applicant has provided step by step instructions to the clinical site for preparing the drug product for infusion.

To preserve cell potency, HPC, Cord Blood is frozen using a controlled rate freezing process and stored in a liquid nitrogen freezer (≤ -150$^{o}$C). The HPC, Cord Blood is placed in a 'overwrap' before being placed in the metal canister for freezing. The Applicant has provided data to validate the freezing, thawing, and washing procedures, and to establish the product dating period, as noted in the Drug Product Stability section above.

**b. Testing Specifications**

Please refer to Table 1 for manufacturer's testing specifications.

**c. CBER Lot Release**

CBER Lot Release testing, including the submission of product samples to CBER, is not required. The basis for this decision is that each REGENECYTE lot is used to treat a single patient. Failure of a single lot will have a minimal potential impact on public health.

**d. Facilities Review / Inspection**

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture and testing of REGENECYTE (HPC, Cord Blood) is listed in the table below. The activities performed and inspectional histories are noted in the table.

**Table 2: Manufacturing Facility for REGENECYTE (HPC, Cord Blood)**

| Name/Address | FEI Number | DUNS Number | Inspection/ Waiver | Justification/ Results |
|---|---|---|---|---|
| StemCyte Inc.<br>13800 Live Oak Avenue.<br>Baldwin Park, CA 91706<br><br>Drug Substance (DS) and Drug Product (DP) manufacturing, DP quality control testing, packaging / labeling, and cryopreservation. | 3003562296 | 162075530 | PLI, 2022 | CBER DMPQ, August 29 - September 2, 2022.<br><br>VAI |

**Acronym key**: BLA – Biologics License Application; CBER – Center for Biologics Evaluation and Research; DMPQ – Division of Manufacturing and Product Quality; DS – Drug Substance; DP – Drug Product; DUNS – Data Universal Numbering System (Dun & Bradstreet); FEI – FDA Establishment Identifier; PLI – Pre-License Inspection; VAI – Voluntary Action Indicated.

CBER conducted a PLI at StemCyte, Baldwin Park, CA facility in late August to early September 2022. A Form FDA 483 was issued at the conclusion of the inspection. The firm's response to the observations and the corrective actions were reviewed and found to be adequate. The inspection was classified as voluntary action indicated (VAI).

**e. Container/Closure System**

The container closure system for the drug product of REGENECYTE (HPC, Cord Blood) is listed below.

**Table 3: Container Closure Components for the REGENECYTE Drug Product**

| Components | Manufacture | Description | Comments |
|---|---|---|---|
| Cryobag | (b) (4) | The cryobag is an integral part to (b) (4) (b) (4) | A 510 (k) cleared product under BK(b) (4) |
| Overwrap Bag | (b) (4) | Ethyl vinyl olefin bag<br>10 cm x 9 cm | Non-product contact |
| Outer Cassettes (frozen use) | (b) (4) | Rigid aluminum cassette<br>3.5" x 4.0" x 0.5" | Non-product contact |

The final product of HPC, Cord Blood is collected into a cryobag that is associated with the 510(k)-cleared single-use (b) (4) The cryobag in

(b) (4) is intended for long-term storage of blood cells in liquid nitrogen per approved 510(k) BK (b) (4) The container closure integrity of the cryobags is checked via a (b) (4) (b) (4) (b) (4) prior to usage. In addition, operators perform visual inspection of the cryopreserved cryobags for cracking or breakage prior to shipping to end users.

**f. Environmental Assessment**

The BLA includes a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The Agency determined that approval of REGENECYTE will not result in any significant environmental impact and concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

**4. Clinical Pharmacology**

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

**5. Clinical/Statistical**

**a. Clinical Program**

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

**Clinical Efficacy Review**

The effectiveness of HPC, Cord Blood for achieving hematopoietic reconstitution has previously been established by FDA analyses of the pooled HPC, Cord Blood dataset of the docket, as well as the COBLT study and other published observational studies. Assessment of hematopoietic reconstitution was based primarily on analyses of neutrophil and platelet recovery of patients who received a suitable allograft (i.e., a total nucleated cell dose (TNC) ≥ 2.5 x $10^7$/kg and ≥ 4/6 degree of human leukocyte antigen (HLA) match). Among the 54 patients, the cumulative incidence of neutrophil recovery defined as absolute neutrophil count (ANC) greater than 500 cells/μL by

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

Day 42 was 91%, similar to that demonstrated in the pooled docket dataset (77%) and in the COBLT study (76%). The median time from transplantation to an ANC greater than 500 cells/μL was 22 days, also comparable to the docket dataset (25 days) and COBLT study (27 days). The cumulative incidence of platelet recovery, defined as a platelet count greater than 20,000 cells/μL by Day 100, was 72%, and the median time from transplantation to a platelet count greater than 20,000 cells/μL was 50 days. Analysis of docket data has indicated that the TNC dose and degree of HLA match are inversely associated with the time to neutrophil recovery. Sixty-six percent (n = 862) of the 1,299 patients in the docket dataset who received a TNC dose ≥ 2.5 x $10^7$/kg underwent transplantation as treatment for hematologic malignancy. Results for patients who received a suitable allograft with REGENECYTE are compared to the hematopoietic reconstitution data from the docket dataset and the COBLT study in Table 4.

The efficacy of HPC, Cord Blood products is assessed in terms of hematopoietic reconstitution in patients who received a suitable cord blood allograft (TNC ≥ 2.5 x $10^7$/kg of recipient weight, and ≥ 4/6 degree of HLA match with patient). The REGENECYTE dataset included 54 patients who received a suitable allograft with 100-day follow-up data. The clinical data, as illustrated in Table 4, provide evidence that transplantation with REGENECYTE results in hematopoietic reconstitution as demonstrated by neutrophil and platelet recovery. The primary graft failure rate for patients receiving a TNC dose ≥2.5 x $10^7$/ kg was 16% in the pooled docket dataset, and 9.3% in patients who received a suitable allograft with REGENECYTE. The REGENECYTE dataset does not include information regarding immunologic reconstitution. However, based on the analyses of the docket data and supported by the publicly available data, HPC, Cord Blood has demonstrated the ability for immunologic reconstitution for patients transplanted for primary immunodeficiency as well as for other malignant and nonmalignant disorders. Considering these data, the review team concludes that this BLA provides substantial evidence that REGENECYTE is effective for the proposed indication.

**Table 4: Summary of Efficacy Demonstrated by Hematopoietic Reconstitution**

| **Data Source** | **Docket and Public Data*** | **COBLT Study*** | **REGENECYTE**** |
|---|---|---|---|
| Design | Retrospective | Single-arm prospective | Retrospective |
| Number of patients, n | 1299 | 324 | 54 |
| Median age in years (range) | 7.0 (<1 - 65.7) | 4.6 (0.07 - 52.2) | 37.5 (0.1 - 70.3) |
| Sex, % | 57% male | 59% male | 48% male |
| Median weight at transplant (range) in kg | NA | NA | 66 (3.0 – 153.3) |
| Median TNC Dose (range) x $10^7$/kg | 6.4 (2.5 - 73.8) | 6.7 (2.6 - 38.8) | 5.8 (2.2 - 34.4) |
| Neutrophil Recovery by Day 42 – (ANC>500/uL), % (95% CI) | 77% (75, 79%) | 76% (71, 81%) | 91% (81%, 97%) |

| Data Source | Docket and Public Data* | COBLT Study* | REGENECYTE** |
|---|---|---|---|
| Platelet recovery by Day 100 (20,000/uL), % (95% CI) | NA | 57% (51, 63%) | 72% (58, 83%) |
| Platelet recovery by Day 100 (50,000/uL), % (95% CI) | 45% (42-48%) | 46% (39-51%) | 73% (54, 88%) |
| Erythrocyte recovery by Day 100, % (95% CI) | NA | 65% (58-71%) | NA |
| Median time to Neutrophil Recovery | 25 days | 27 days | 22 days |
| Median time to Platelet Recovery (20,000/uL) | NA | 90 days | 50 days *** |
| Median time to Platelet Recovery (50,000/uL) | 122 days | 113 days | 64 days *** |
| Median time to Erythrocyte Recovery | NA | 64 days | NA |

*Data from patients who received a suitable allograft (TNC ≥2.5 x $10^7$/kg and ≥4/6 HLA match)
**Note that evaluable data for outcomes were not available for all patients and there are various amounts of missing data. Forty-four (44) patients had evaluable data for median TNC dose (from units > 2.0 x$10^7$) and 38 patients had evaluable data for platelet recovery ≥ 50,000/μL (excludes 16 patients with missing data).
*** Eleven (11) patients (20%) died before platelet recovery. They were imputed with the longest recovery time in the analysis.
NA: data not available
In the REGENECYTE dataset, the number of days to neutrophil or platelet engraftment assumes 30.4 days per month. The cumulative incidence and 95% CI are presented for neutrophil recovery by day 42 and platelet recovery by day 100.

Assessment of efficacy in the BLA review is based on voluntary data collection, and evaluable data for outcomes were not available for all patients in the REGENECYTE dataset. While the data suggest favorable trends in favor of REGENECYTE, the data are insufficient to support its superior effectiveness due to limitations of the retrospective dataset. Comparisons of the applicant's dataset to the COBLT and docket datasets are limited by the following factors: incomplete and missing data from retrospective observational data (including insufficient information about the nature and severity of the diseases that were the primary indications for transplantation and the conditioning regimens) and demographic differences between the applicant's dataset and the docket and COBLT study.

**b. Pediatrics**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and

effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. The active ingredient, indication, dosage form, dosing regimen, and route of administration of REGENECYTE, are not new because they are the same as for the first FDA-approved HPC, Cord Blood, HEMACORD, manufactured by New York Blood Center. Therefore, this application does not trigger PREA.

### c. Other Special Populations

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

## 6. Safety and Pharmacovigilance

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

### a. Infusion Reactions

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

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

**Table 5: Incidence of Infusion-Related Adverse Reactions Occurring in >1% of Infusions in the COBLT Study**

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

Information on infusion reactions was available from voluntary reports for 54 patients who received suitable allografts with at least a single unit of REGENECYTE. Table 6 shows that the incidence of infusion reactions with the applicant's product is comparable to the COBLT data. Preparative regimens and GVHD prophylaxis were not standardized. The reactions were not graded for severity. The most common infusion reactions with the applicant's product were hypertension (3.7%), nausea (1.9%), and vomiting (1.9%).

**Table 6: Incidence of Infusion Reactions**

| Infusion Reactions | COBLT Infusions with a TNC Dose ≥2.5 x $10^7$/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

**b. Other Adverse Reactions**

For other adverse reactions (i.e., other than infusion reactions), the raw clinical data from the dockets were pooled for 1,299 patients (120 adult and 1,179 pediatric) transplanted

with HPC, Cord Blood (from multiple cord blood banks) with TNC ≥2.5 x $10^7$/kg. Sixty-six percent (n=862) underwent transplantation as treatment for hematologic malignancy. The preparative regimens and graft-versus-host disease prophylaxis varied. The median TNC was 6.4 (range, 2.5 - 73.8) x $10^7$/kg. Limited data on other adverse reactions were also available for patients treated with REGENECYTE.

**i. Deaths (Day 100 mortality)**

For the 1,299 patients in the pooled docket dataset, Day 100 mortality from all causes was 25%. For the 54 patients who received a suitable allograft with REGENECYTE, Day 100 mortality from all causes was 13%, and the most common causes of death were organ failure (5.4%), infection (3.7%), and primary disease (1.9%).

**ii. Primary Graft Failure**

Primary graft failure occurred in 9.3% of patients in the REGENECYTE dataset. This is comparable to the 16% incidence of primary graft failure in the docket data.

**iii. Graft-versus-Host Disease (GVHD)**

For patients in the pooled docket dataset who received a TNC dose ≥2.5 x $10^7$/kg, the incidence of acute GVHD was 69%: grades 2-4 GVHD was 42%, and grades 3-4 GVHD was 19%. Data for acute GVHD in the REGENECYTE dataset was available for 54 patients who received a suitable allograft. Of these patients, 31 (57.4%) experienced acute GVHD. Chronic GVHD was reported in 11 (20.4%) patients in the StemCyte dataset.

**iv. Engraftment Syndrome (ES)**

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

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

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

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

Therefore, the package insert gives precedence to this pooled, publicly available safety data over the REGENECYTE safety 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 sponsor will conduct routine pharmacovigilance in accordance with 21 CFR 600.80. However, to monitor the postmarketing safety of the product, the review team recommends a postmarketing safety outcomes monitoring and analysis plan, and expedited reporting of serious infusion reactions [see 11(c)].

## 7. Labeling

The proposed proprietary name, REGENECYTE, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on October 11, 2022, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on November 18, 2022.

APLB reviewed the proposed prescribing information (PI) and carton/container labels on January 10, 2024, and found them acceptable from a promotional and comprehension perspective.

## 8. Advisory Committee Meeting

This application was not referred to the Cellular, Tissue, and Gene Therapies Advisory Committee because the information submitted in the BLA, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

## 9. Other Relevant Regulatory Issues

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

## 10. Recommendations and Benefit/Risk Assessment

### a. Recommended Regulatory Action

The review team recommends approval of REGENECYTE as indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment. The benefit risk assessment for an individual patient depends on the patient

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

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

**b. Benefit/Risk Assessment**

The benefit of REGENECYTE is based on hematopoietic and immunologic reconstitution in patients with disorders of the hematopoietic system. Considering the substantial risks associated with HPC, Cord Blood, the benefit-risk assessment is highly individualized. The benefit-risk assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.

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

REGENECYTE is expected to have a favorable benefit-risk profile.

**c. Recommendation for Postmarketing Activities**

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

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

   a. maintenance of an observational database to include, for all REGENECYTE units released, information including but not limited to, time to neutrophil recovery, graft failure, survival, cause of death, infusion reactions, and other adverse experiences;

   b. aggregate analyses of interval and cumulative adverse experience reports; and

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

ii. Submit a 15-day alert report for each serious infusion reaction associated with administration of REGENECYTE.