Office of Biostatistics and Epidemiology/Division of Epidemiology
Pharmacovigilance Review Memo

BLA/Supplement Number:	125413/0
Product Name:	AlloCord (Hematopoietic Progenitor Cells – Cord)
Sponsor:	SSM Cardinal Glennon Children's Medical Center
Indication(s):	in conjunction with an appropriate preparative regimen for use in hematopoietic stem cell transplantation procedures for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment
Applicant:	Saint Louis Cord Blood Bank (SLCBB)
Date(s):	CBER receipt date: 10/21/2011; PDUFA date: 08/20/2012
Review Priority:	Standard (10-month)
From:	Damon Green, MD, MS Medical Officer, Therapeutics and Blood Safety Branch (TBSB), Division of Epidemiology (DE), Office of Biostatistics and Epidemiology (OBE)
Through:	Michael Ngyuen, MD Acting Chief, TBSB, DE, OBE

1. Introduction

OBE/DE/TBSB has completed a Mid-cycle review of BLA STN 125413 for AlloCord (Hematopoietic Progenitor Cells – Cord) by St. Louis Cord Blood Bank (SLCBB). The purpose of this review is to evaluate the potential safety issue involving transfusion reactions, to assess the adequacy of the proposed pharmacovigilance plan (PVP) and the possibility of post-market safety studies for safety monitoring should this product be licensed. Information on the clinical studies and safety data in this review are derived from the Sponsor's Licensing Application (BLA). Words in *Italics* are quoted from this BLA.

2. Product Background

Transplantation of hematopoietic progenitor cells has been considered experimental, though lifesaving therapy for rare genetic/ hematologic diseases, the first transplants occurring in 1993. *The SLCBB was established in 1995 as a joint effort of SSM Cardinal Glennon Children's Medical Center and the St. Louis University School of Medicine. Intending to create an inventory of cord blood stem cells to restore hematopoiesis in patients unrelated to the donor and to export the products across state lines, the SLCBB voluntarily submitted an Investigational New Drug application in 1997.* From 1998 to 2000, the FDA solicited data (clinical, non-clinical, laboratory), comments, and proposals from interested stakeholders, in an effort to establish standards that could ensure the safety and effectiveness of cord blood products used in transplantation therapy nationwide. This information now exists in a public docket (Docket No. FDA-2006-D-0157), and has since been used to complete the "Final Guidance for Industry: Minimally Manipulated Unrelated Allogeneic Placental/ Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications," published in 2009, and used as a guidance for cord blood licensure.

SCLBB's…*cord blood collections are manipulated to reduce red cells and plasma using BioE'sPrepaCyte®-CB processing system. The final product is contained in ----------(b)(4)---------- bag to which a volume of cryoprotectant solution resulting in 10% final dimethyl sulfoxide (DMSO) concentration is added* (NOTE: the cryoprotectant is a mixture of DMSO and Dextran-40). *The bag is protected from cross contamination ----------(b)(4)----------, placed in an ---(b)(4)--- canister, and frozen -------(b)(4)---------- before being transferred into liquid nitrogen for long term storage.*

Hematopoietic Progenitor Cell – Cord (HPC-C) blood products are indicated in conjunction with an appropriate preparative regimen for use in hematopoietic stem cell transplantation procedures for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment;

As noted in the Cellular, Tissue, and Gene Therapies (CTGT) Advisory Committee meeting Briefing Documents (meeting held on September 22, 2011), the hematopoietic stem and progenitor cells contained in an HPC-C product, after infusion to an appropriately prepared ("conditioned") recipient, regenerate and replace the recipient's

blood and immune system. Overall, allogeneic hematopoietic stem cell transplantation, a) allows treatment of malignancies, after high doses of radiation and chemotherapy, through reconstitution with new, healthy hematopoietic cells. The reconstituted system can also exert an immunologic effect on the remaining malignant cells and prevent relapse; or b) in cases of genetic diseases, transplantation replaces the patient's defective cells with healthy ones that provide normal proteins (e.g. hemoglobin or immunoglobulins) or normally functioning enzymes that can restore the recipient's defective systems.

3. Clinical Studies

No prospective clinical trials were conducted with AlloCord. The safety review for this product is based on voluntarily reported adverse events and an outcomes dataset generated by the Stem Cell Therapeutic Outcomes Database (SCTOD) and submitted by the sponsor.

4. Safety Database

4.1 Safety Outcomes Dataset

Data related to patient outcomes is obtained directly from transplant centers through a series of forms designed for data capture at specific time points, or from SCTOD, which is administered by the Center for International Blood and Marrow Transplant Research (CIBMTR) – a combined research program of the Medical College of Wisconsin and the National Marrow Donor Program (NMDP). *Since 2008 greater than 98% of patient outcomes data reported to the SLCBB comes directly from CIBMTR.* Noted limitations of this registry data *include a limited data set with regard to reported variables (i.e.: infection information post transplant is not available), timeliness of reporting, and availability of patient outcomes from international transplant centers.*

Units manufactured between 1/1/1996 and 11/2/2009, were processed under the ----(b)(4)---- methodology. Of these units, (b)(4) products have been exported for single unit transplantation. Since 11/3/2009, units have been manufactured with PrepaCyte®-CB. To date, (b)(4) units have been exported for transplantation, though data is available for only (b)(4) patients.

4.2 Adverse Event: Infusion reactions

Of the -----(b)(4)----- manufactured units, data was missing for (b)(4) transplants. Of the (b)(4) units remaining, 602 had adverse event data from which 64 (11%) units had a reported infusion reaction. The list of reactions included bradycardia, dyspnea, emesis, fever, hematuria, hypertension, and rash. For the (b)(4) PrepaCyte manufactured units, no adverse events have been reported.

According to SLCBB Standard Operation procedure (SOP) QM.04.04 (Occurrence Report Policy), a Serious Adverse Event (SAE) *represents a significant medical hazard and includes any event that: is fatal, is life-threatening (immediate risk of death),*

requires or prolongs hospitalization, is disabling or causes permanent injury, is a new malignancy, or necessitates medical or surgical intervention. No SAEs were reported for SCLBB products.

5. Pharmacovigilance Planning

5.1 Potential risks

Infusion reactions are known, common events, and usually mild; The Cord Blood Transplantation Study (COBLT) – a dataset with prospective clinical monitoring for infusion reactions, comprised data for 511 patients receiving 523 cord blood units, resulting in 65% of infusions associated with any reaction, and 4 (0.8%) cases reported as an SAE with cardiopulmonary symptoms. Ruiz-Delgado, et al. Dimethyl sulfoxide-induced toxicity in cord blood stem cell transplantation: report of three cases and review of the literature, Acta Haematol., 2009, reported the incidence of any cord blood infusion reaction ranging from 4% to 65%, with life-threatening infusion reactions occurring in up to 4.6% of patients.

Severe infusion reactions are thought to be attributed to the cryopreservative and/or dilutional agents DMSO or Dextran-40 which are necessary in preparation of cord blood units, and are also used in SCLBB products. Known side effects of Dextran are renal failure, pulmonary edema, congestive heart failure, coagulopathy, and anaphylactoid reactions. Side effects of DMSO include hypernatremia, fluid overload, dysgeusia, nausea, vomiting, elevated liver enzymes, hemolysis, renal failure, and allergic reaction.

SLCBB outcomes data, though largely reported by registry (SCTOD) since 2008, has been passively reported with delineated forms prior to that time, having notable missing data. Though the adverse event reporting rate is consistent with the literature, and no SAEs for SLCBB products have been noted, under-reporting or under-estimation of the risk must be considered.

5.2 Proposed Pharmacovigilance Plan (PVP)

SLCBB intends to conduct routine monitoring and adverse event reporting as written in its SOP, QM.04.04 (Occurrence Report Policy), which references the FDA Guidance for Industry: MedWatch Form FDA 3500A: Mandatory Reporting of Adverse Reactions Related to Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) – a guidance for adverse event reporting required by 21 CFR 1271.350(a).

In addition, *"The Stem Cell Therapeutic and Research Act of 2005 established the CW Bill Young Transplantation Program. Under this Program, the Stem Cell Therapeutic Outcomes Database (SCTOD) administered by the CIBMTR, was charged with collecting, analyzing and reporting on outcomes of all allogeneic transplants in the US, including CB* (cord blood) *transplants. CIBMTR must also provide accrued data to the CB Banks in electronic format monthly."* This collection from and reporting of

outcomes data to the cord blood banks is required and under the direction of the Health Resources and Services Administration (HRSA). The focus of the CIBMTR data collection is clinical outcomes; however, some information on infusion reactions may be reported by transplant centers. According to the "Overview of CIBMTR Cord Blood Data Collection Program" submitted by the sponsor: "*Although real-time data collection of adverse events related to cord blood transplantation is not the purpose of the observational data systems of the CIBMTR, summary information about infusion-related adverse events is collected by the CIBMTR and is provided to banks as a tool for verification of adverse event reporting associated with cord blood units. Data regarding infusion-related adverse events is collected in summary fashion on the infusion form for validation and research purposes, and is not meant to replace real-time AE reporting by HCT centers to the CBCC or the originating bank or registry."* Use of SCTOD helps avoid duplicate efforts as "*Using the centralized platform of the CIBMTR brings value to cord banks by streamlining data collection to a single, cooperatively developed mechanism which collects standardized data elements with quality monitoring in the setting of required reporting. Banks receiving outcome reports can focus on analysis of the data for the benefit of their manufacturing processes, without being burdened by development of their own data collection processes. Transplant centers who use cord blood products for hematopoietic transplantation benefit from a universal data collection system and processes that avoid redundant data submission that is burdensome and error-prone, provide validation closer to the source of the data, and are accompanied by education efforts targeted to improving data quality*."

Thus, SCLBB must report basic cord blood unit information to SCTOD (CIBMTR), who then is required to report accrued outcomes data back to SCLBB monthly. Such reporting mechanisms may facilitate more complete and accurate outcome and exposure data than is currently available.

6. Assessment and Recommendations

1. No clinical studies evaluating the risk of infusion reactions (serious or non-serious) specific to SLCBB cord blood units were submitted, and the infusion safety data presents a concern for under-reporting and under-estimation due to passive reporting and missing data. Lack of true denominator data and missing information inhibit the calculation of true incidence rates and the reliability of the dataset.

With an adverse event reporting rate consistent with background literature, and having no SAEs reported, severe infusion reactions are likely rare and the strength of association with SLCBB products is likely low.

2. Although SLCBB has an established SOP for routine monitoring and adverse event reporting, it references a guideline instructing reporting for only communicable disease related adverse events (21 CFR 1271.350(a)). In order to include other adverse events (i.e. Infusion reactions), reporting according to 21 CFR 600.80, as outlined in the Final Guidance for Industry: Minimally Manipulated Unrelated Allogeneic Placental/

Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications, published in 2009, should be required.

Because each cord blood unit released for infusion is linked to a specific, matched patient, communication between the Cord Blood Center and the infusing center is enhanced over routine passive surveillance. Given this aspect of the product as well as the already established statutory requirements for adverse event reporting by Transplant Centers under the *CW Bill Young Transplantation Program* (SCTOD), adverse event reporting as required by 21 CFR 600.80 will be sufficient for addressing the concern of infusion reactions. Additional follow-up information to elucidate possible association between AlloCord and infusion reactions can be requested from the sponsor as part of root cause analysis of any serious infusion reactions reported to FDA.

3. No post-marketing studies appear necessary at this time; although, section 505(o) of FDA Amendments Act (FDAAA) authorizes the FDA to require post-marketing studies or clinical trials after approval, should the FDA become aware of new safety information that suggests a higher or more severe risk of serious infusion reactions with AlloCord than was known at the time of approval.

4. Although they are labeled events, the FDA should require expedited reporting of all serious infusion reactions with AlloCord.

5. FDA regulations required quarterly Periodic Adverse Experience Reports (PAERS) to contain a narrative summary and analysis of the information in the report and an analysis of the 15-day Alert reports submitted during the reporting interval (21 CFR 600.80(c)2). The narrative summary in PAERs for AlloCord should include a detailed summary and assessment of all serious infusion reactions observed during the reporting period, as well as the sponsor's assessment of each case and the overall frequency of serious infusion reactions since approval and during the reporting period. The sponsor should also include any adverse event information forwarded from SCTOD to the sponsor during the reporting period (e.g., infusion reaction or other adverse event information). PAERs should also include the number of units released for infusion and the number of patients receiving infusions with AlloCord during the reporting period.

6**.** Exposure to DMSO and Dextran-40, though not completely avoidable, can be limited by proper preparation before infusion of cord blood. Warnings and instructions for preparation (e.g. thawing, washing, dilution) should be included in the label.

Letter comments for communication to the sponsor:

None at this time.