Summary Basis for Regulatory Action

Date: May 24, 2012

From: Yong Fan, MD

BLA/ STN#: 125391

Applicant Name: ClinImmune Labs, University of Colorado Cord Blood Bank

Date of Submission: May 2, 2011

PDUFA Goal Date: June 2, 2012 (original date of March 2, 2012 extended 3 months by Major Amendment)

Proprietary Name/ Established Name: None

Non-Proprietary name: HPC, Cord Blood

Indication: HPC, Cord Blood is an allogeneic cord blood hematopoietic progenitor cell therapy intended for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment**.** The risk benefit assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority:

Celia Witten, PhD, MD, Office Director, OCTGT

□ I concur with the summary review.
□ I concur with the summary review and include a separate review to add further analysis.
□ I do not concur with the summary review and include a separate review.

Mary Malarkey, Director, Office of Compliance and Biologics Quality

□ I concur with the summary review.
□ I concur with the summary review and include a separate review to add further analysis.
□ I do not concur with the summary review and include a separate review.

Material Reviewed/ Consulted Specific Documentation Used in Developing the SBRA

CMC Review	22-May-2012: Fan, Bi, Abbasi, Ghosh, Karandish
CBER Lot Release	23-May-2012
Facilities Review	22-May-2012: Heidaran
Environmental Assessment	07-Feb-2012: Heidaran
Nonclinical Pharmacology/Toxicology Review	06-Feb-2012: Hoque
Clinical and Statistical Joint Review (safety and efficacy)	23-May-2012: Witten, Haudenschild, Cheng
Advertising and Promotional Labeling Review	27-Apr-2012: Nguyen
DCEPT Division Director Memo	23-May-2012: Bryan

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1. Introduction

Biologics License Application (BLA) STN#125391 is for HPC, Cord Blood manufactured by the ClinImmune Labs, University of Colorado Cord Blood Bank (UCCBB). HPC, Cord Blood is an allogeneic cord blood hematopoietic progenitor cell therapy indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.

The risk-benefit assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.

The applicant followed FDA guidance recommendations and cited Docket 1997N-0497 for the efficacy data to support this application. The BLA includes the applicant's safety outcomes dataset to support the safety of the product.

This document summarizes the basis for the approval of HPC, Cord Blood. 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

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). This guidance provides recommendations for the submission of a BLA for placental/umbilical cord blood. 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. On May 2, 2011, ClinImmune Labs, University of Colorado Cord Blood Bank submitted a BLA application to request licensure of HPC, Cord Blood.

The applicant's original BLA submission proposed an indication statement consistent with the FDA licensure guidance. However, on September 22, 2011, the Cellular, Tissue, and Gene Therapy Advisory Committee met to discuss a BLA for a related product. After consideration of the proceedings of that meeting, ClinImmune Labs revised the proposed indication statement to the following: 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.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

Product Description

HPC, Cord Blood is manufactured by ClinImmune Labs, University of Colorado Cord Blood Bank. The manufacture of HPC, Cord Blood at ClinImmune Labs, University of Colorado Cord Blood Bank is consistent with recommendations made in the FDA licensure guidance.

Mothers who consent to donate their newborn's cord blood for public banking are screened and tested for communicable infectious diseases per regulations in 21 CFR 1271 Subpart C. Cord blood is collected from mothers who screen and test negative for the relevant infectious disease markers. A positive CMV result is allowed, and the CMV result will be reported to the transplant center when the lot of HPC, Cord Blood is selected. The applicant has arrangements with five hospitals in Colorado and Arizona and a state-wide remote collection program to collect cord blood. The collected cord blood units (CBU) are transported to the ClinImmune Labs by dedicated couriers using validated and temperature-monitored shipping containers.

HPC, Cord Blood is processed by volume reduction and partial red blood cell (RBC) and plasma depletion. ----------(b)(4)----------. The final product is in 30-124 ml total volume containing 10% DMSO and 1% Dextran 40. Each lot is frozen using a -----(b)(4)----- freezing process and then stored in either vapor or liquid phase of liquid nitrogen ($\leq$ -150^{o}C). The final product is tested for purity, identity, sterility, and potency. HPC, Cord Blood will have a 5-year dating period from the date of cryopreservation.

HPC, Cord Blood is shipped frozen in special shipping containers (dry-shippers) designed to maintain a controlled environment and a very low temperature ($\leq$ -150^{o}C). Shipping must be completed within (b)(4) and temperature is electronically monitored and recorded for the entire transit time.

The thawing and preparation procedures have been validated. Directions for thawing are appended to the end of the prescribing information in the section "Instructions for Preparation for Infusion", and will be included with each shipped lot of HPC, Cord Blood.

Manufacturing Controls

Process and product controls are in place to assure the quality of HPC, Cord Blood. There are specified time limits for all manufacturing process steps; cord blood is processed and frozen within -(b)(4)- of collection. Lot release is based on a combination of in-process

testing results as well as final product testing. A summary of the lot release tests performed on each lot of HPC, Cord Blood is shown in Table 1. Infectious disease testing is performed on a maternal blood sample; hemoglobin analysis and ABO/Rh typing are performed on pre-processing cord blood samples; and the rest of the testing is performed on post-processing cord blood samples. All lot release tests must meet specifications for the product to be released into the search inventory. Confirmatory HLA typing is performed on an attached segment at the time of release for transplantation.

Table 1: ClinImmune Labs Lot Release Acceptable Criteria for HPC, Cord Blood

Product Characteristics	Testing/ inspecting	Sample Type	Acceptance Criteria
Safety	Infectious disease [21 CFR 1271.45-90]	On maternal blood sample within 7 days of birth. [21 CFR 1271.80(a)(b)]	All tests negative, except non-treponemal test for syphilis when confirmatory test is negative. CMV results are recorded.
	Sterility- Bacterial/fungal cultures	(b)(4) sample post processing	No growth
	Hemoglobin	Donor (Baby) Blood	----------(b)(4)----------
Integrity	Container, closures, seals	Intact	Visual cord blood bag inspection
Purity and Potency	Total nucleated cells (TNC)	HPC, Cord Blood (pre-cryopreservation)	> 5.0 x 10^8 TNC/unit HPC, Cord Blood
	Viability of TNC	HPC, Cord Blood (pre-cryopreservation)	(b)(4)
	Viable $CD34^+$ cell count	HPC, Cord Blood (pre-cryopreservation)	≥ 1.25 x 10^6 viable CD34+ cells/ unit HPC, Cord Blood
	-------(b)(4)----------	----------(b)(4)----------	-(b)(4)-
Identity	HLA typing	Cord Blood (pre-processing) and HPC, Cord Blood segment (Confirmatory HLA typing on attached segment)	Test Report
	ABO and Rh	Cord Blood pre-processing and RBC sample post processing	Test Report

Manufacturing Risks

The greatest risks associated with the manufacture of the HPC, Cord Blood are 1) the risk of transmitting infectious diseases, 2) the risk of product contamination, particularly during collection of the cord blood and also during processing, and 3) the potential for loss in product potency during cryostorage or thawing. These risks are mitigated/minimized by various approaches.

To address infectious disease risks, medical records are reviewed for high-risk exclusions, and mothers of the newborn donors are also screened and tested for infectious diseases according to 21 CFR 1271 regulations. Cord blood collection is performed in delivery suites. The collection staff are trained to use aseptic technique and appropriate gowning, and collect one cord blood unit at a time.

Each collected cord blood unit is given a unique bar code ID number (ISBT 128) which is both machine and manually readable. This bar code is associated with all test results (maternal and cord blood) as well as the matched patient data.

To address contamination risks, collection and processing personnel are trained appropriately. The processing methods have been validated to ensure aseptic processing, and the cryoprotectant is added to the processed HPC, Cord Blood using aseptic technique within a biosafety cabinet. Post-processing samples are tested for microbial contamination and must be negative.

To preserve cell potency, HPC, Cord Blood is frozen using a -----(b)(4)----- freezing process and then stored in either vapor or liquid phase of the liquid nitrogen freezer ($\leq$-150^{o}C). HPC, Cord Blood is placed in a (b)(4) 'overwrap' bag before being placed in the metal canister for freezing.

The applicant has provided data to validate the freezing and thawing procedures and to establish the product dating period. Based on the stability data submitted to the BLA, the current dating period for HPC, Cord Blood is 60 months (5 years).

b) CBER Lot Release

An exemption has been granted from CBER Lot Release testing, including no requirement for submission of product samples to CBER. The basis for this decision is the fact that each lot is a single HPC, Cord Blood unit that will treat a single patient. Lot release testing would negatively impact the limited quantity of cells available to the patient, and failure of a single lot will have a minimal potential impact on public health.

c) Facilities review/inspection (DMPQ)

The Center for Biologics Evaluation and Research (CBER) conducted a Pre-License Inspection (PLI) at ClinImmune Labs manufacturing facility located in Aurora, Colorado (FEI number 3000719146) from August 22 – 26, 2011. The PLI focused on the following:

Quality Systems, Facility and Equipment Systems, Materials Management Systems, Production Systems, Packaging and Labeling Systems, and QC Laboratory Control Systems used to manufacture and provide quality controls for the HPC, Cord Blood, in addition to the process and control for Donor Eligibility. The inspection team reviewed and verified the documents related to donor eligibility, facility and equipment qualification, process validation, aseptic process validation, environmental monitoring, quality systems, QC laboratory controls, production, shipping validation, computer systems, and training. In addition, the inspection team observed the entire operation for processing HPC, Cord Blood, which included receipt, accessioning, processing, cryopreservation, QC testing, storage, packaging and shipping.

A Form FDA 483 was issued at the conclusion of this PLI on August 26, 2011. Ten objectionable conditions were noted on the Form FDA 483 documenting deficiencies mainly in quality practices, aseptic process validation and batch record documentation. Following issuance of the Form FDA 483, ClinImmune implemented corrective actions that adequately address the ten objectionable conditions.

d) Environmental Assessment

ClinImmune Labs requested a categorical exclusion from an environmental assessment pursuant to 21 CFR 25.31 (c), which applies to a biologic product containing substances that occur naturally in the environment when the introduction of the product does not alter significantly the concentration or distribution of the substances, their metabolites, or degradation products in the environment. The request for categorical exclusion is justified because the product meets the applicable exclusion criteria in 21 CFR Part 25, and there is no information indicating that extraordinary circumstances exist.

4. Nonclinical Pharmacology/Toxicology

No preclinical pharmacology/toxicology studies were conducted with HPC, Cord Blood due to the minimal manipulation of the product and the previous human experience with HPC, Cord Blood (from multiple cord blood banks).

5. Clinical Pharmacology

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

6. Clinical / Statistical

a) Clinical Program

This BLA was submitted by ClinImmune Labs and proposes to use HPC, Cord Blood 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 HPC, Cord Blood and references data in the dockets FDA-1997-N-0010 and FDA-2006-D-0157. The clinical review also considered the available scientific literature and the results of the Cord Blood Transplantation (COBLT) study. Although the data from the clinical experience with HPC, Cord Blood had substantial limitations, the review team determined that the BLA submission was sufficient for assessment of the safety and efficacy of HPC, Cord Blood.

Clinical efficacy review:

The effectiveness of HPC, Cord Blood, as defined by hematopoietic reconstitution, was demonstrated in one single-arm prospective study (COBLT), and in retrospective reviews of data from an observational database for HPC, Cord Blood manufactured by ClinImmune Labs and data in the dockets and public information. Sixty-six percent (n=862) of the 1299 patients in the docket and public data underwent transplantation as treatment for hematologic malignancy. Results for patients who received a total nucleated cell dose $\geq 2.5 \times 10^7$/kg are shown in Table 2. Neutrophil recovery is defined as the time from transplantation to an absolute neutrophil count more than 500 per microliter. Platelet recovery is the time to a platelet count more than 20,000 per microliter. Erythrocyte recovery is the time to a reticulocyte count greater than 30,000 per microliter. The total nucleated cell dose and degree of HLA match were inversely associated with the time to neutrophil recovery in the docket data.

Table 2: Hematopoietic Recovery for Patients Transplanted with Total Nucleated Cell (TNC) Dose ≥ 2.5 x 10^7/kg

Data Source	The COBLT Study*	Docket* and Public Data*	ClinImmune Labs HPC, Cord Blood
Design	Single-arm prospective	Retrospective	Retrospective
Number of patients	324	1299	220
Median age (range)	4.6 (0.07 – 52.2) yrs	7.0 (<1 – 65.7) yrs	6.9 (0.1 – 73.1) yrs
Gender	59% male 41% female	57% male 43% female	57% male 43% female
Median TNC Dose (range) (x 10^7/kg)	6.7 (2.6 – 38.8)	6.4 (2.5 – 73.8)	5.8 (2.5 – 65.0)
Neutrophil Recovery at Day 42	76% (95% CI 71% – 81%)	77% (95% CI 75% – 79%)	79% (95% CI 73.5% – 84.4%)
Platelet Recovery at Day 100 (20,000/uL)	57% (95% CI 51% – 63%)	-	62% (95% CI 44.8% – 77.5%)
Platelet Recovery at Day 100 (50,000/uL)	46% (95% CI 39% – 51%)	45% (95% CI 42% – 48%)	55% (95% CI 36.0% – 72.7%)
Erythrocyte Recovery at Day 100	65% (95% CI 58% – 71%)	-	-
Median time to Neutrophil Recovery	27 days	25 days	25 days
Median time to Platelet Recovery (20,000/uL)	90 days	-	55 days
Median time to Platelet Recovery (50,000/uL)	113 days	122 days	49 days
Median time to Erythrocyte Recovery	64 days	-	-

* HPC, Cord Blood (from multiple cord blood banks)

The primary graft failure rate for subjects receiving a TNC dose ≥2.5 x 10^7/ kg was 16.4% in the pooled docket dataset, and 19.5% in clinical experience with HPC, Cord Blood. The clinical data, as illustrated in Table 2, provides evidence that transplantation of HPC, Cord Blood results in hematopoietic reconstitution as demonstrated by neutrophil, platelet, and erythrocyte engraftments. Considering these data, the review team concludes that this BLA provides substantial evidence that HPC, Cord Blood is effective for the proposed indication.

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. This application does not trigger PREA.

c) Other Special Populations

Clinical experience with HPC, Cord Blood did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently to HPC, Cord Blood than younger subjects.

7. Safety

The safety review considered the data in the docket, the dataset for the COBLT study, and published literature; these safety data are based on clinical experience with HPC, Cord Blood (from multiple cord blood banks). The safety assessment of HPC, Cord Blood was also based on a review of the outcome dataset of 499 patients transplanted with 542 HPC, Cord Blood units manufactured by ClinImmune Labs for treatment of a variety of clinical indications. The safety review focused on 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

The data described in Table 3 reflect exposure to 442 infusions of HPC, Cord Blood (from multiple cord blood banks) in patients treated using a total nucleated cell dose $\geq 2.5 \times 10^7$/kg on a single-arm trial (The COBLT Study). The population was 60% male, and the median age was 5 years (range 0.05-68 years), and included patients treated for hematologic malignancies, inherited metabolic disorders, primary immunodeficiencies, and bone marrow failure. Preparative regimens and graft-vs-host disease prophylaxis were not standardized. The most common infusion reactions were hypertension, vomiting, nausea, and bradycardia. Hypertension and any grades 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 3: Incidence of Infusion-Related Adverse Reactions Occurring in ≥1% of Infusions (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
Hemogloburia	2.1%	0
Hypoxia	2.0%	2.0%

ClinImmune Labs defined infusion reactions as events usually associated with HPC, Cord Blood infusions and occurring within 24 hours of transplantation. Information on infusion reactions was available from voluntary reports for 47 patients who received HPC, Cord Blood manufactured by ClinImmune Labs at a total nucleated cell dose $\geq 2.5 \times 10^7$/kg. The population included 72% males and 28% females, with median age 12 years (range 0.4 - 67.5 years). Preparative regimens and graft-vs-host disease prophylaxis were not standardized. Seventeen patients (36%) had an infusion reaction. Infusion reactions included hypertension (11%), nausea (8%), vomiting (4%), facial flushing (4%), hypoxia (2%), headache (2%), fever and chills (2%), hematuria (2%), and bradycardia (2%).

b) Adverse Reactions other than Infusion Reactions

For other adverse reactions (i.e., other than infusion reactions), the raw clinical data from the docket were pooled for 1299 patients (120 adult and 1179 pediatric) transplanted with HPC, Cord Blood (from multiple cord blood banks) with total nucleated cell dose $\geq 2.5 \times 10^7$/kg. Sixty-six percent (n=862) underwent transplantation as treatment for hematologic malignancy. The preparative regimens and graft-vs-host disease prophylaxis varied. The median total nucleated cell dose was 6.4 (range, 2.5 - 73.8) x 10^7/kg. Data on other adverse reactions were also available for 208 patients treated with HPC, Cord Blood manufactured by ClinImmune Labs, at a total nucleated cell dose $\geq 2.5 \times 10^7$/kg.

- Deaths (Day-100 mortality)

  For the 1299 patients in the pooled dataset, Day-100 mortality from all causes was 25%. Primary graft failure occurred in 16%. For the 208 patients in the ClinImmune dataset, Day-100 mortality from all causes was 36%. The proportions of subjects who died by Day 100 varied significantly by indication, ranging from 3% to 36% for those who received a TNC dose $\geq 2.5 \times 10^7$/kg. The most common causes of death with HPC, Cord Blood were infection (26.5%), organ failure (16.1%), and graft failure (11.5%).

- Graft-versus-Host Disease (GVHD)

  For subjects in the pooled docket dataset who received a TNC dose $\geq 2.5 \times 10^7$/kg, the incidence of grades 2-4 GVHD was 42%, and of grades 3-4 GVHD was 19%. Data regarding GVHD occurrence are available for 43 patients who received HPC, Cord Blood manufactured by ClinImmune Labs at a TNC dose $\geq 2.5 \times 10^7$/kg. Of those 43 subjects, 44% developed acute GVHD, and 12% developed chronic GVHD.

- Engraftment Syndrome (ES)

  The data in the docket do not address the risk of ES. In addition, the BLA does not include any reports of ES associated with HPC, Cord Blood manufactured by ClinImmune Labs. However, 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%.

- 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 docket 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. The data are not sufficient to support reliable estimates of the incidences of these events. The BLA did not include any reports of donor cell leukemia, transmission of serious infection, or transmission of rare genetic disorders associated with HPC, Cord Blood manufactured by ClinImmune Labs.

Due to differences in the size and quality of the datasets, the review team assessed the safety data from the pooled docket and other publically available data as the best indicator of the likely post-marketing performance of HPC, Cord Blood. Therefore, the package insert gives precedence to this pooled, publically available safety data over the HPC, Cord Blood safety data.

8. Advisory Committee Meeting

This application was not referred to an Advisory Committee because the product is not the first-in-class and the review committee did not identify novel concerns.

9. Other Relevant Regulatory Issues

This BLA did not include a proposed pharmacovigilance plan. Considering the extensive prior clinical experience with HPC, Cord Blood (from multiple cord blood banks), the review team determined that a pharmacovigilance plan was not necessary. In addition, review of the BLA did not identify any safety concerns that were not already known for this class of product. Therefore, the BLA review does not include a Pharmacovigilance Plan Review from the Office of Biostatistics and Epidemiology. However, to monitor the post-marketing safety of the product, the review team recommends a post-marketing safety outcomes monitoring and analysis plan, and expedited reporting of serious infusion reactions.

10. Labeling

The package insert (PI) originally submitted to the BLA and all subsequent amendments related to the label were reviewed by members of the BLA review team. Multiple discussions about the PI were held between review team members and the applicant. These discussions resulted in multiple rounds of revisions until final agreement was reached. The most significant discussions and changes related to incorporating a class labeling approach for HPC, Cord Blood products, are summarized below:

- The originally proposed indication statement was withdrawn and replaced with a new proposed indication statement.

- A boxed warning was added regarding the risks of infusion reactions, GVHD, engraftment syndrome, and graft failure, each of which can be fatal.

The applicant did not submit a request for a proprietary name.

The Advertising and Promotional Labeling Branch reviewed the package insert, patient labeling, and carton and container labels. Changes to container and package labels were required in order to be in full compliance with regulations. After discussions with the applicant, all of these submissions were found to be acceptable.

The sponsor will submit the label in Structured Product Labeling format after product licensure.

The proposed label provides adequate directions for the safe and effective use of HPC, Cord Blood in the indicated population.

11. Recommendations and Risk / Benefit Assessment

a) Recommended Regulatory Action

The review team recommends approval of HPC, Cord Blood 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 risk benefit assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.

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

b) Risk / Benefit Assessment

The benefit of HPC, Cord Blood 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 risk benefit assessment is highly individualized.

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.

c) Recommendation for Postmarketing Risk Management Activities

There was no safety issue identified that warrants a Risk Evaluation and Mitigation Strategy (REMS). HPC, Cord Blood is expected to have a favorable risk-benefit ratio.

d) Recommendation for Postmarketing Activities

There are no safety issues that warrant post-marketing requirements or commitments.

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

1. Implement a safety outcomes monitoring and analysis plan. This plan will include a) maintenance of an observational database to include, for all HPC, Cord Blood units released, information including but not limited to, time to neutrophil recovery, graft failure, survival, cause of death, infusion reactions, and other adverse experiences, b) aggregate analyses of interval and cumulative adverse experience reports, and c) safety outcomes analyses of interval and cumulative data that address early mortality, graft failure-related mortality, graft failure, time to neutrophil recovery, infusion-related events, and other adverse experiences. Reports will include a description of the population analyzed, results of the analyses, whether outcomes indicators were triggered and, if so, what actions were implemented as a result.

2. Submit a 15-day "alert report" for each serious infusion reaction associated with administration of HPC, Cord Blood.