Acknowledgment of Filing Letter, November 8, 2011 - Ducord

Our STN: BL 125407/0
Duke University School of Medicine
Carolina Cord Blood Bank
Attention: Bruce Burnett, Ph.D.
Director, Regulatory Affairs
Hock Plaza, 2424 Erwin Road, Suite 402
Durham, NC 27705

Dear Dr. Burnett:

This letter is in regard to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act.

We have completed an initial review of your application dated September 8, 2011 for *Hematopoietic Progenitor Cells, Cord (HPC-C)* to determine its acceptability for filing. Under 21 CFR 601.2(a) we have filed your application today. The review goal date is July 9, 2012. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

We will contact you regarding your proposed labeling no later than June 9, 2012. If post marketing study commitments (506B) are required, we will contact you no later than June 9, 2012.

While conducting our filing review, we identified the following potential review issues:

1. Please provide the following SOPs for review:

    a. CT2-SOP-002: -----(b)(4)----- for CD34+/---(b)(4)---,

    b. SOP describing emergency product recovery plan, and

    c. SOP describing review of medical records including physical examination documents for both the birth mother and baby (fixed and non-fixed collection sites).

2. Please provide additional information regarding the following validation studies:

    a. For the following analytical assays performed by the CCBB Processing Laboratory including:

(1) (b)(4) for CMV,

(2) ---(b)(4)--- for viability, and

(3) TNCC: Proficiency data for CCBB personnel using --(b)(4)-- instrument.

b. For the following analytical assays performed by Duke Stem Cell Lab:

(1) (b)(4), and

(2) Viable CD34+.

c. For the following analytical assays performed by Robertson Clinical Translation Lab:

(1) TNCC Viability,

(2) CD34+ viability, and

(3) (b)(4).

d. Validation or performance proficiency and personnel training data for analytical assays performed by contract testing laboratories including:

(1) Infectious disease testing (----------(b)(4)----------);

(2) HLA typing (----------(b)(4)----------); and

(3) Hemoglobinopathy (NC State Laboratory of Public Health, New England Newborn Screening Program).

3. Please provide additional information so that we can evaluate your Stability protocol and expiration date proposal:

a. Please submit a table containing information on a sampling of individual HPC-C units used to assess stability: 1) Unit number, 2) when infused, 3) manufacturing process, 4) where manufactured and stored, 5) analytical methods used to assess units.

b. Different assays were performed by different laboratories to assess pre- and post-thaw product quality attributes. Demonstration of comparability between these various assay methods and laboratories is necessary to assess the

stability data. Please provide comparability data for analytical methods used for pre/post thaw analyses, including:

(1) Viability assays: ----(b)(4)---- (at CCBB) vs. (b)(4) assay (Robertson Clinical Translation Lab);

(2) TNCC: Using --(b)(4)-- instrument (at CCBB) vs TNC analysis using -----(b)(4)----- reagents (at Robertson Clinical Translation Lab);

(3) CD34+ cell quantitation using ----(b)(4)---- system (at Duke Stem Cell Lab) vs CD34+ and -(b)(4)- enumeration assay using -----(b)(4)----- reagents (at Robertson Clinical Translation Lab); and

(4) (b)(4) performed at Duke Stem Cell Lab vs. Robertson Clinical Translation Lab.

4. Please provide more information/clarification on the following sections of the validation report for the sterility testing performed using the ---(b)(4)--- system (Module 3, Part 3.2.S.4.3.4):

a. For Phase I of your validation study you have indicated that “an inoculum containing (b)(4) CFU/ml was injected using sterile technique into a set of culture bottles” and “a second set of culture bottles was inoculated using an inoculum of (b)(4) CFU/ml”. Please indicate the total number of CFUs injected per culture bottle (absolute number) and update the respective Phase I data tables as necessary.

b. For Phase II of your validation study you have indicated that -------- (b)(4)-------- were combined. Please indicate the ratio of each fraction in the combined test article. Also, please indicate how much of this combined test article was actually inoculated per culture bottle along with the test microorganisms.

c. The data tables for the Phase II study indicate the inoculum size in CFU/ml. Please indicate the total number of CFUs inoculated per culture bottle (absolute number) and update the respective Phase II data tables as necessary.

5. We note that you include a “pre-activated” electronic temperature logger in the collection kit that is sent to the birth mother for cord blood collection at non-fixed sites. Please provide SOP(s) describing the following:

a. Acceptable temperature ranges for storage of the collection kit by the birth mother and shipment of the cord blood unit from the collection hospital to the processing laboratory.

b. The quality control performed on the temperature loggers.

6. Please provide the CLIA number for the infectious disease testing laboratory.

7. Please provide information about how birth mothers are assessed for the possibility of plasma dilution prior to the collection of donor testing specimens in order for the donor eligibility determination to be made as specified in 21 CFR Part 1271.80(d)(2). Please submit applicable procedure(s) and/or form(s).

8. Please provide clarification regarding the test kits used for the screening of donors for syphilis:

a. Treponemal donor screening testing -----(b)(4)----- System (------(b)(4)------) listed in section 3.2S.4.2.1, Table S4.2.1-1; and

b. Non-treponemal screening test (b)(4) (no manufacturer information provided) listed in SOPs CCBB-COL-002, CCBB-COL-025 and CCBB-LAB-018.

9. Please provide additional information regarding the “confirmatory” and “ discriminatory” tests listed in the following SOPs and explain whether or not these test results are factored into the donor eligibility determination:

a. CCBB-LAB-018, section 8.1.3: HBc and HTLV I/II confirmatory tests, and

b. CCBB-LAB-020, section 8.3.2.8: HIV-1, HCV and HBV discriminatory tests.

10. You have submitted the donor eligibility SOP (CCBB-COL-002) and the Exclusion and Quarantine Release form in the batch records (#5 - #8). However, we are unable to determine from these documents when the final donor eligibility (DE) determination, based on the results of donor screening and testing is performed, and whether or not information regarding DE determination is included in the search database. Please clarify this procedure and provide any SOP(s) that contain this information.

We are providing the above comments to give you preliminary notice of **potential** review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we shall advise you in writing of any action we have taken and request additional information if needed.

If you have any questions, please contact the Regulatory Project Manager, Mark L. Davidson, at (301) 827-6536.

Sincerely yours,

Raj K. Puri, M.D., Ph.D.
Director
Division of Cellular and Gene Therapies
Office of Cellular, Tissue, and Gene Therapies

Page Last Updated: 11/02/2012
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