DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

March 26, 2015

Our STN: BL 125585/0

BLA FILING NOTIFICATION

Puget Sound Blood Center and Program Cord Blood Services
Attention: Rebecca Haley, M.D.
921 Terry Avenue,
Seattle, WA 98104

Dear Dr. Haley:

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 January 15, 2015 for Hematopoietic Progenitor Cells (HPC), Cord Blood, to determine its acceptability for filing. Under 21 CFR 601.2(a) we have filed your application today. The review goal date is January 28, 2016. 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.

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

PRODUCT INFORMATION

1. We note that section 3.2.S.2.5.2 "Cord Blood Processing, Automated Validation" intends to serve as a process validation summary of pre- and post-processed "Quality Parameters" and includes data on (b) (4) HPC, Cord Blood units processed on (b) (4) devices (i.e., (b) (4) . Please respond to the following related items:

   a. Table S.2.5.1-5 (CFU Summary) includes two data sets for (b) (4) HPC, Cord Blood units (i.e. (b) (4) Please clarify the significance of the additional data.

   b. Table S.2.5.1-6 (Overwrap and Bag Label Acceptability) indicates that (b) (HPC, Cord Blood units (i.e., (b) (4) were processed on both (b) (4) instruments, however preceding tables only have data for these units after processing on one

(b) (4) instrument. Please clarify if data for all of your tested "Quality Parameters" (e.g. TNC, Viability, CD34+, CFA) was collected on these units after processing on both (b) (4) instruments.

c. We note that your Appendix (i.e. Table A.5.6-1 Cord Blood Services Critical Equipment and Instrument Inventory) lists (b) (additional (b) (4) Please clarify the status of these additional instruments with regard to your process validation.

2. We note you submitted a "(b) (4) Thaw Summary Report" that includes data intended to serve as process validation summary for your thawing process. Please respond to the following related items:

a. We also note that your proposed "Preparation for Infusion" user instructions indicate that thawed HPC, Cord Blood units may be stored at (b) (4) for up to (b) (4) if product is not diluted or up to (b) (4) if thawed and diluted with (b) (4) Please provide the sampling times and temperature range details of your (b) (4) Thaw Summary Report" to clarify that your thawing process validation addresses all aspects of your proposed "Preparation for Infusion" user instructions.

b. We note you do not indicate a cryoprotectant removal wash step in your proposed "Preparation for Infusion" user instructions. However, please clarify if your (b) (4) Thaw Summary Report" included cryoprotectant removal on thawed HPC, Cord Blood units. Please note that your validation data summary should address cryoprotectant removal for use in transplant centers that perform this step. For additional information please see "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," (http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM357135.pdf).

3. We note (reference - Sterility Test Validation, Section 3.2.S.4.3.2.1A: (b) (4) Addendum.pdf) that you performed the method suitability test (product-mediated inhibition test) using just (b) (4) of the HPC, Cord Blood (b) (4) . As your proposed test sample volume is (b) (4) of HPC, Cord Blood (b) (4) (total) of test microorganisms (b) (4) of test media and submit the data for our review.

4. We note that section 3.2.P.8.1 "Stability Testing, Evaluation and Protocol" reported stability data on (b) (4) random representative HPC, Cord Blood units from 2012 that were thawed and tested for post-processing acceptance criteria. Please clarify the post-thaw

handling conditions (e.g. processing duration, temperature range details, etc.) and/or reference the appropriate SOP that was followed during your stability evaluation.

5. Based on the package label (label applied at time of distribution to the cassette that contains the HPC, Cord Blood) that you have submitted, it appears that you have not fully implemented the ISBT 128 labeling system. As you have stated in your exemption request from the barcode labeling requirements, ISBT 128 specifies a standard layout for the product label. In order for the agency to consider your exemption request, please submit the final package label after you have fully implemented the ISBT 128 labeling system.

6. Please submit the CLIA certificate for the laboratory that performs donor infectious disease testing.

7. It is unclear from the submitted materials how the actual elapsed shipping and handling times along with the ambient temperature conditions encountered for cord blood shipments compare to your shipping plan and the validated conditions of the containers used for shipping cord blood. Please provide the actual elapsed shipping times and expected surrounding temperature conditions from the collection sites to the manufacturing site, and clarify how these actual shipping conditions lead to your designation of what shipper ((b) (4) is used.

FLOW CYTOMETRY INFORMATION

8. You stated that (b) (4) ". Please submit your proposed validation plan in detail.

9. You stated "Qualification of the (b) (4), Operational Qualification was performed by employee (b) (4) and reviewed by employee (b) (4). Training on the test case(s) and other applicable documentation for employee (b) (4) was documented in the Tester Training section of the protocol. Employee (b) (4) did development work on the procedures and was author and validation coordinator of the Qualification. Training was conducted and documented in conjunction with these activities (Section 3.2.S.4.3.3.1)". However, it appears that multiple operators participated in your validation studies. Please provide more details about the training records for all users who participated in your proposed validation studies.

10. Please revise your SOP to include that the CD34+ HPC result will considered valid if the data obtained from the (b) (4) is less than (b) (4) of the CD34 + HPC results. We also recommend that you include an investigational plan that will be performed in case that the level exceeds the (b) (4) limit.

11. Based on Test case 5 (hold time) results, please update CBP 6210 to indicate that the maximum hold time for the sample is (b) (4)

12. For Test Case 4 CD34, (b) (4) precision, you stated that (b) (4) operators set up (b) (4) replicate assay sets per lot of (b) (4)) and per time point (two time points), and data analysis is based on Analysis of Variance (ANOVA)". We have the following comments:

    a. Table S.4.3.3-12 gives result summary based on (b) (4) data points. With (b) (4) operators setting up (b) (4) replicate assay sets per lot of (b) (4)) and per time point (b) (4) time points), this will result in a total of (b) (4) data points. Please clarify the number of data points included in this analysis.

    b. Table S.4.3.3-12 provides mean, standard deviation, and coefficient of variation (CV) for each of CD34, (b) (4) You stated that the difference is small enough that it would not negatively affect the results of the (b) (4) assay within observed operational limits. However, no criterion was specified to evaluate what you mean "difference is small enough". Please clarify.

    c. Precision data for (b) (4) viability is missing in Addendum#1. Please submit the missing data for our review.

13. For CD34 and (b) (4) accuracy, please submit the missing data regarding the third lot used in your proposed validation study.

14. Regarding Test case 1- CD34 accuracy, we noted mismatched lot numbers between the data submitted in Addendum#1 and table S.4.3.3-9. Please correct the typo error.

15. We note in Table S.4.3.3-11b (Test Case 3- Accuracy of Viability Stain) that the HPC, Cord Blood Unit (b) (4) was used twice. Based on the data submitted in Addendum#1 (Change Control # 67812), the HPC Cord Unit should be (Unit # (b) (4)) and Operator's IDs should be (b) (4) . Please correct the typo error.

16. Regarding Test Case 6- (b) (4) Linearity please provide the following:

    a. We recommend that you specify the number and type of controls used in your proposed Linearity study for (b) (4), CD34 and (b) (4).

    b. It appears that your proposed formulas to calculate the expected (b) (4), CD34 and (b) (4) counts were inappropriate and mismatched with your expected data results submitted in Addendum#1. Please revise your formulas to reflect the correct expected counts for your validation studies.

FACILITY INFORMATION

17. Please provide the addresses for your collection sites and collection partners.

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, Ramani Sista, at 240 402 8354.

Sincerely yours,

Raj K. Puri, M.D., Ph.D.
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