AI Letter, October 28, 2011 - HPC Cord Blood

Our **STN: BL** 125391/0
Clinimmune Labs
Attention: Sharon Miller
12635 East Montview Blvd, Suite 300
Aurora, Colorado 80045
Dear Ms. Miller:
We are reviewing your biologics license application (BLA) dated April 29, 2011 including amendments dated June 28, and September 27, 2011, for Hematopoietic Progenitor Cells (HPC), Cord Blood and have determined that the following information is necessary to take complete action. Please promptly submit your written response to the following items so that we may continue evaluating your BLA:

PRODUCT MANUFACTURE

1. Please submit the collection validation, --(b)(4)-- processing validation, and -----(b)(4)----- freezer validation as discussed during inspection and previous teleconferences.
2. Please provide validation outcome of the "large" shipping container for the shipment of the collected CBUs for processing.

STABILITY AND EXPIRATION DATE

3. Please provide your stability testing protocol and summary.
4. Please ensure that the samples you use for your stability study represent both ----------(b)(4)------ methods.
5. Please include TNC recovery, CD34 recovery, viability, (b)(4) assay and sterility tests in your product stability study.

PRODUCT TESTING

6. Please submit the cell count and -----(b)(4)----- viability test validations as discussed during inspection.

STERILITY ASSAY VALIDATION

7. We note that you provided data on the “media suitability” aspect of your proposed sterility assay but did not test for the bacteriostatic/fungistatic property in the final test article, in your ----------(b)(4)----------. Please test for the bacteriostatic/fungistatic property of the ----------(b)(4)---------- by the following method and recommendations and submit the data for our review:

a. Please inoculate each ----------(b)(4)---------- culture bottles with less than 100 CFU (absolute number) of test microorganisms and ----------(b)(4)---------- processed from whole cord blood units, and incubate the bottles in the ------(b)(4)------ instrument as per ---(b)(4)--- recommendation to find the minimum time to detection (all detection times should be reported as number of hours).

b. Your panel of test microorganisms should include the five previously used microorganisms (coagulase negative ----------(b)(4)----------) and the following classes

of microorganisms: i) aerobe (----------(b)(4)---------- Micrococcus luteus), ii) spore forming bacteria (Bacillus subtilis), iii) mold (-------(b)(4)-------) and iv) slow growing fungi (----------(b)(4)----------).

c. We recommend that you use culture bottles inoculated with less than 100 CFU (absolute number) of test microorganisms but without ----(b)(4)----, as positive controls as this to interpret the data in case the ----------(b)(4)---------- has any species-specific bacteriostatic/fungistatic property.
d. Please ensure that the --------(b)(4)--------- used in this study are processed from whole cord blood units and using the same processing method and reagents as described in your BLA application.
e. Please ensure that none of the donor mothers of the used cord blood units were on antibiotics preceding the collection, as this could adversely affect the results of the study.
f. For this study, please incubate all bottles until growth is detected or until 14 days.

8. Please describe how you have assessed the ruggedness and robustness of your proposed sterility test method. For guidance please refer to our rapid microbiology sterility test validation draft guidance document (Draft Guidance for Industry: Validation of Growth-Based Rapid Microbiological Methods for Sterility Testing of Cellular and Gene Therapy Products, 2008; http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072612.htm).
9. It is unclear if you are using a graph of level of ---------(b)(4)--------- for analyzing the positivity/negativity of the sample using the ------(b)(4)------ instrument – if yes, please provide representative graphs for typical positive, typical negative and questionable cultures.

DONOR ELIGIBILITY

10. Based on the information you have provided for collections at non-fixed sites, we understand that the maternal risk questionnaires are sent to the donor in advance and are self administered. According to the DE guidance (section IV.C), the donor history interview is defined as a documented dialogue concerning the donor's medical history and relevant social behavior. Please explain when the completed questionnaires are reviewed with the donor and provide applicable SOPs.
11. In your response letter dated September 16, 2011, you indicated that at the time of collection at non-fixed sites, the birth mother completes an abbreviated health update. Please explain how the birth mother determines whether or not there are any changes in the health history. For example, do you provide a copy of the maternal risk questionnaires that the mother had completed initially?
12. The IQ/OQ/PQ documents that you have submitted for the donor infectious disease testing validation are not adequate. At minimum, the validation should demonstrate that the test kits work the way they are supposed to at the contract testing laboratory with various operators (e.g. recent proficiency records).
13. Please clarify the following in SOP C1.200.4, section entitled "Recipients & Donors: Confirming & Documenting Risk":

a. Is confirmatory testing (CMV (b)(4), Hep C virus (b)(4) and HIV-1 and HIV-2 (b)(4)) performed on a thawed sample of all units collected prior to May 25, 2005 and

those released outside of the NMDP? If yes, please specify that units will be used under an IND.

b. Please explain why the donor risk assessments listed on pages 5 and 6 do not include all the risks listed on the NMDP Maternal Risk Questionnaire action form and the risk factors assessed during the review of medical and physical examination records.

14. Please submit the SOP that describes how the birth mother's medical records are obtained for collections performed at non-fixed sites. According to the Cord Blood Collection Agreement, the clinician agrees to provide only the baby's medical records.
15. Please clarify whether or not the maternal blood specimens are processed prior to shipment to the contract testing laboratory (refer to SOP D9.200.6, step 5). If they are processed in your laboratory, please provide the SOP.
16. On the HPC, Cord Blood Batch Unit Release Report, the following information was absent:

a. There is no designated section for the cord blood unit ID#.
b. Final donor eligibility determination not documented.

Please submit the revised form.

17. Please provide the following information that was requested during the teleconference on 10/3/11:

a. Please revise the following SOPs to clearly identify the infectious disease tests that you currently perform:

- C1.100.3: NAT HIV/HCV, (b)(4), NAT HBV not listed, (b)(4) listed instead of (b)(4)
- C1.200.4: NAT HBV not listed
- C1.110.4: HIV (b)(4) and ---(b)(4)--- for HIV listed

a. Please submit the revised SOP(s) that clearly defines the criteria for assessment of the birth mother for possibility of plasma dilution prior to obtaining the infectious disease testing specimens.

MANUFACTURE FACILITIES

18. In regard to HVAC qualification, provide a detailed revalidation/validation document to confirm that the system performance is within the predetermined accepted criteria for relevant parameters including differential pressure and air volume exchange per hour.
19. The Environmental Monitoring program Performance Qualification study was not conducted to assess the initial facility environmental monitoring status for all classified areas. Please clarify.
20. Shipping validation of the container used for transport of product from the firm to transplant centers is incomplete in that the validation study was not performed using the worst case scenario. Specifically the shipping container was validated statically and not during an actual shipment of the product or its surrogate. Please clarify.
21. Please provide documentation supporting that the current computer system used at ClinImmune is Part 11 compliant. Provide a copy of SOP B9.430.3 and B9.450.1 describing the procedure for data entry.
22. Provide information on your plans to segregate the cord blood IND units from the licensed product.

CLINICAL

23. Please provide your SOP that describes how you collect and manage the safety data, and your plan to ensure the quality of the collected data.

Please submit your response in a timely manner or submit a partial response, so we may continue the review of your application. If we determine that your response to this information request constitutes a major amendment, we will notify you in writing. If we receive your major amendment during the last three months of the review period, we will extend the review period an additional three months. We are continuing to review all the sections of your application.

If you have any questions, please contact the Regulatory Project Manager, Ramani Sista, at (301) 827 5152.

Sincerely yours,

/s/

Raj K. Puri, M.D., Ph.D.
Director
Division of Cellular and Gene Therapies
Office of Cellular, Tissue, and Gene Therapies
Center for Biologics Evaluation and Research