Filing Review Letter, July 15, 2011 - HPC Cord Blood

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health
Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

STN: 125391/0

Clinimmune Labs
Attention: Sharon Miller
12635 East Montview Blvd, Suite 300
Aurora, Colorado 80045

Dear Ms. Miller:

Please refer to your biologics license application (BLA), submitted under section 351 of the Public Health Service Act, and to our filing letter dated July 3, 2011. While conducting our filing review we identified the following potential review issues:

PRODUCT INFORMATION

Manufacture-Raw Material Qualification:

1. You stated that your quality unit approves/rejects all components, however, your SOP B8.200.6 indicated that all qualification tests are performed by the operational staff, quality unit is notified only when there is an abnormal test result, please clarify.

Manufacture-Processing SOPs

2. The SOPs D2.200.8 and D2.100.9 include the following statement: “Cords that do not meet the release criteria will be reviewed by a Lab Director or Medical Director and can be considered for permanent storage if validated”. Please explain the inventory management of the CBUs that do not meet release criteria and under what circumstances you will release these CBUs.

Manufacture-Process validation:

3. We note that many of the “retrospective” validations in your submission are retrospective data analysis instead of validation studies performed following validation protocols with predefined acceptance criteria. Our evaluation of your retrospective validation reports is further complicated by your use of mean values as your acceptance criteria, and that you combined the validation proposal and validation summaryin the same document. We feel you need to perform processing and assay validations according to the recommendations of the following guidance documents:

a. Process Validation: General Principles and Practices http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf
b. Analytical Procedures and Methods Validation http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070489.pdf

4. On page 31 of the CMC section, the post thaw viability ranges reported by the transplant centers were ----------(b)(4)----------. Please provide the explanations of the low viabilities and how you plan to ensure that the units with such low viabilities will not be released from your bank.

Manufacture-(b)(4) new software validation (B6 113A, 9/10/09)

5. Please provide MNC recovery, CD34+ cell recovery and sterility data.

Manufacture-(b)(4) new kit validation (B5 113.1, 9/10/09)

6. Please provide MNC recovery, CD34+ cell recovery and sterility data.

Validation of Thaw and Wash Procedure

7. ----------(b)(4)----------.
8. ----------(b)(4)----------.
9. Please provide sterility data.
10. The post thaw CD34+ cell recoveries were low, and your explanation is that the samples were not always analyzed immediately. Please provide CD34+ cell recovery data on the samples that were analyzed immediately post-thaw to confirm that the low recoveries were indeed caused by delay in sample analysis.

Manufacture----(b)(4)----- Freezer Validation

11. (b)(4) data were not provided, as the results are stated to be pending since 2006. Please explain whether or not the (b)(4) analysis was performed and completed.

Manufacture-Stability Program:

12. On page 51 of the CMC section, you report mean post thaw viability for the (b)(4) units of cord blood stored for (b)(4) was (b)(4). Please submit a detailed description of the thawing and testing methods. Please clarify whether or not the cells were washed after thaw. If ----------(b)(4)---------- was used as a test method for viability, please include the final concentration of --(b)(4)--, the time between thaw and performance of the viability assay, the incubation time after adding the ---(b)(4)--, and indicate the number of operators that performed this stability study.
13. You evaluated bag integrity based on ----------(b)(4)----------. We are concerned that this method is not sensitive enough to detect slow leakages due to minor defects that could compromise the product safety and quality. We recommend you develop a bag integrity test method of greater sensitivity with respect to bag leakage.

STERILITY TEST AND METHOD VALIDATION INFORMATION

We note that you have used three different protocols for assessing the sterility of your cord blood samples (2005-2007, 2007-2010 and 2010-Current). Please submit the following items for all three protocols.

14. Please submit a detailed Standard Operating Procedure (SOP) for your sterility assay using your ---(b)(4)--- culture system. The SOP should indicate:
    a. The distribution of personnel responsibilities for the following activities -
        i. sample inoculation
        ii. loading/unloading of inoculated bottles in/from the ---(b)(4)--- device
        iii. monitoring, analyzing, signing and reporting of test results
        iv. quality control of media
        v. maintenance and trouble-shooting of the culture system
        vi. records keeping
    b. Equipment and supplies used.
    c. Step-by-step procedures for sample inoculation and incubation.
    d. List all aseptic techniques used during the process.
    e. Describe procedures for reading and reporting positive, negative and abnormal sterility culture results.
    f. Provide details of your shipping method (for example - shipping temperature, time and method for monitoring the temperature during shipping) for samples sent to a contract testing lab.
15. Please submit details of your microbial species identification method used when samples are positive for microbial growth.
16. Please submit the following information pertaining to your ---(b)(4)--- device:
    a. Brief description of the device and its working principle

b. Complete location information
c. Device serial number
d. Device installation qualification (IQ) and operation qualification (OQ) reports
e. Incubation temperature and humidity level used (please indicate the respective tolerance limits)

17. Please submit complete composition of all microbial culture media (used during the actual sterility assay and during assay validation), their qualification methods and indicate the frequency of qualification testing.
18. In the event you plan to retest a sterility-positive sample if you find the sterility test run is invalid, please submit details describing the retesting procedure.
19. Regarding ----(b)(4)---- Method Validation (Form B5.113.2): Please indicate the source of the microbes used in your validation study.

TESTS AND TEST VALIDATIONS (IN addition TO TESTS FOR STERILITY AND CD34+) INFORMATION

20. You state that the UCCBB has set up an agreement with the Colorado Department of Health (DOH) to obtain the hemoglobinopathy testing results on the EDTA baby's blood collected at day 3 and confirmed at 4 weeks after birth, indicating only abnormal results are confirmed by the UCH Clinical Special Chemistry Laboratory. However you have only provided hemoglobinopathy test validation information for the verification purpose performed at UCH Clinical Special Chemistry Laboratory. Please provide detailed test validation information including the SOP and results of studies that serve to validate the hemoglobinopathy test performed at Colorado Department of Health (DOH) on the EDTA baby's blood.
21. The SOP for ABO and Rh testing performed at University of Colorado Hospital does not indicate how the test results are interpreted and recorded. Please provide details.
22. You state in your BLA submission that you plan to license all cord blood units collected since July 20, 2005. In this case, please submit all the test validation information generated since July 20, 2005. If the tests were performed at different lab facilities or different test methods used, please submit the test validation information for each individual test method performed at each facility. The following are examples when your validation data did not completely cover your proposed license date of July 20, 2005:
    a. For your "Total Nucleated Cells Test" validation, you stated in your "Retrospective Validation of ----------(b)(4)---------- for Use with Hematopoietic Progenitor Cells (HPC)" that the initial validation by Clinimmune of the instrument was performed after a move to BioScience Place (BSP) and calibration on August 28, 2006.
    b. Your "Viable Nucleated Cells" validation was initiated from September, 2006.
    c. For your "HLA Typing" validation, the SOP for "----------(b)(4)----------" was issued on August 10, 2009.
    d. Although the original SOP for ABO and Rh testing performed at University of Colorado Hospital was provided, the test validation documentation was issued on October 15, 2010 and was indicated as retrospective validation.

e. The validation of (b)(4) assay was issued on April 30, 2007.

----------(b)(4)---------- VALIDATION

23. Your SOPPs and validation studies for -------(b)(4)----- include instructions, data, and data analysis for cell types other than HPC-C. Please revise these to focus solely on HPC-C.
24. Please provide the analysis of the ----(b)(4)---- data including the -----(b)(4)----- and number of HPC-C samples.
25. Please provide product information and certificates of analysis of ----------(b)(4)----------.
26. Please provide certificates of analysis for both CD34 and (b)(4) antibodies. Information provided should demonstrate analytical specificity and analytical sensitivity for CD34 and (b)(4) reagents.
27. The manufacturer claims an analytical sensitivity of -----(b)(4)----- for CD34 antibody. Please determine the effective range for the University of Colorado's Clinical laboratory using both ----------(b)(4)----------.
28. Please provide further information on the -----(b)(4)----- software including a description of the software and how it is used in evaluation of Cord Blood products, with appropriate plots of ------(b)(4)------ data.
29. Please provide more information for the CD34 Enumeration Kit including the product insert and detailed description of the components of the kit and directions for use.
30. In the section titled OPERATIONAL (PERFORMANCE), QUALIFICATION AND DESCRIPTION, please clarify the term "(b)(4)".
31. Please define "-(b)(4)-". Is it an isotype control?
32. Please provide examples of appropriate plots for ----------(b)(4)---------- as used in CD34 analysis of cord blood.
33. We note the method to calculate checksum (Calculated CD34/ml/ Absolute CD34/ml) in the calculations and filing section. Please explain how these calculations are done? Also, please provide a copy of result sheet with CD34 ----------(b)(4)----------, as it is filed.
34. Please confirm that the CD34 enumeration kit is the only kit used for stem cell enumeration. If you propose to use different kits, please provide validation data for each.
35. In your validation studies you compared two different instruments using the same samples. Since the second instrument was used later you accepted a viability cut off of (b)(4). Please justify this.
36. In your validation studies you compared two different instruments. The (b)(4) consistently detected more CD34 stem cells. You explain that the positive bias in (b)(4) was due to -----(b)(4)------ which may lead to higher numbers since the (b)(4) include more CD34 dim cells. Please perform instrument comparisons using ----(b)(4)---- only.

DONOR ELIGIBILITY INFORMATION

37. 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).
38. For collections at non-fixed sites, we understand that the maternal risk questionnaire is completed by the birth mother in advance. Since several of the questions are related to specific time frame, please specify how far in advance of delivery the questionnaire may be completed in order to be considered valid for use in making donor eligibility determination.
39. Please submit Forms C1.111 (Collection Hospital Maternal Physical/Health Assessment) and C1.112 (Collection Hospital Newborn Physical/Health Assessment).
40. Please confirm whether you utilize the "NMDP Action Form for recommendations of risk assessment" as part of your donor eligibility determination procedure (SOP C1.110.3) and submit a copy of the NMDP document.
41. Please clarify whether you use a treponemal specific or non-treponemal specific donor screening test for syphilis and how you determine the donor eligibility based on the results. We have noted the following contradictory information in the SOPs and other submitted documents. Please resolve discrepancies.
    a. In CMC section 4.6.1 and in SOP D9.200.4, you indicate that you are using the ----------(b)(4)---------- plate (manufactured by -----(b)(4)-----) for syphilis testing. However, in SOP C1.110.3 (page 5), it is stated that if initial (b)(4) results are reactive, the donor is eligible if confirmatory testing is negative. If you are using the treponemal specific screening test, then the donor must be determined to be ineligible, if test result is positive or reactive. If you are using a non-treponemal screening test and a specific treponemal confirmatory test, please provide the test kit and manufacturer information.
    b. In SOPs C1.110.3, page 7, D9.200.4, pages 1, 2, 10 and 11, Syphilis/(b)(4) is listed under the maternal Infectious Disease Testing Review section.
    c. In SOP C1.110.3, page 11, step 11, it is stated that the unit is discarded if there is positive infectious disease test even if confirmatory testing is negative.
42. Please confirm that from 9/12/07 to 1/2/2008, you were using ----------(b)(4)---------- for syphilis testing. We note that this is not a FDA cleared donor screening or diagnostic serologic test for syphilis.
43. Please clarify whether testing for --(b)(4)-- has been performed on all donors since Jan 2, 2008. In SOP C1.110.3, page 5, it is listed as one of the maternal donor tests but in SOP D9.200.4, page 11, it is listed as an optional test.
44. We note that you have listed NAT HBV as an optional test and discard units with reactive results. Please provide the test kit and manufacturer's information.

DMPQ INFORMATION

45. In a table format, provide the following information for the cord blood units (CBU) to be licensed since July of 2005:
    a. Identification number of CBU's to be licensed;
    b. Date of processing for each unit;
    c. Location/facility of processing and if the facility and equipment were qualified;

d. Classification of the processing rooms;
e. Methods of collection, processing and cryopreservation and if aseptic process validation was performed;
f. Equipment or devices used in collection, processing, testing and cryopreservation (indicate if a non 510(k) cleared equipment/device is used);
g. Test methods and contract laboratories used (including donor eligibility testing).

46. Provide policies/procedures for sample retention.
47. Provide qualification summary reports for the major and minor utility systems used in the ClinImmune facility that affect the cord blood manufacturing area or process.
48. The Executed Batch Record provided is a summary of test results for each unit. Please provide a copy of the Master Batch Record and a sample of the working Batch Record. Batch production and control record must be prepared for each HPC-C and must include complete documentation of each significant step in the manufacture, processing, packing or holding of each unit.
49. Provide rationale why aseptic processing validation including media fill studies was not performed and additionally, provide information how you demonstrated the closed state of the (b)(4) system.
50. Provide information on your plans to segregate the cord blood IND units from the licensed product.
51. In regard to movement of stored cord blood from your processing facility to the storage facility, provide a summary report of the transport/shipping validation.
52. Provide SOPs used for line/room clearance and changeover.
53. Provide an overview of the off site storage facility and any equipment and utilities associated with the storage of the cord blood units.
54. Correct the FEI # for the main facility located on page 6 of the ClinImmune Labs, University of Colorado Cord Blood Bank Item 3: Summary.
55. Clarify what claim of categorical exclusion you are applying for 21 CFR Part 25.31 either (a) or (c).

CLINICAL INFORMATION

56. Please provide the following information for review : consent form C2.102; consent form C2.106 and consent form C2.109

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 (301) 827 5152.

Sincerely yours,

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