Thomas, Terrolyn

From: Thomas, Terrolyn
Sent: Wednesday, June 15, 2011 3:50 PM
To: Quinley, Eva; Zdanowski, Michael J; Streun, Ed
Subject: OUTSTANDING ISSUES: BLA 125397

Hi:

Attached are outstanding issues that need to be addressed as soon as possible, preferably by next week. We would like to set up a telecon to discuss the outstanding issues, please choose one of the following times:

Monday, June 20 - 11-12PM or 1-2PM

PROCESSING

1. In Table 7 under Process Validation Report, NCBP-VAL-10-012R1, page 15, the mean CD34 cells/HPC value is less than the minimum value. On verification during the pre-approval inspection in April 2011a transcription error was observed. You agreed to revise and resubmit the revisions to the file. Please submit the revisions the agency for review. These discussions were with DR, Tao Wang.
2. In your Process Validation Protocol, NCBP-VAL-10-012P, page 5, you report that some characterization and testing of HPC-Cs during the execution of the validation were performed at (b)(4). Please clarify what testing was conducted at (b)(4)
3. Please define how long the retentions samples are kept; refer to the Section VII.B.14.f. of the Cord Blood Licensure Guidance for information on how long retains may be kept. We note that you report that they are kept indefinitely.
4. We note that some of your SOPs describe procedures for other samples, e.g. Flow cytometry procedures. We recommend that SOPs for cord blood processing pertain to cord blood alone.
5. Per the regulations cited in 21 CFR 211.137 and 21 CFR 1271.260, the HPC-C product must bear an expiration date determined by appropriate stability testing. Please describe how the HPC-C expiration date will be attached to the product. We note that you have established a 4 year expiration for HPC-C prepared by manufacturing method 4.

DONOR ELIGIBILITY AND COLLECTION

6. Please resolve the following outstanding issues and provide the revised documents that you had indicated in your responses to the questions discussed at the teleconference on 4/11/11 and the pre-license inspection:

   i. "Report on Matched Cord Blood Unit (CBU)" addressing the footnote "FDA approved assays" which is not applicable to the tests performed on the cord blood sample.
   ii. Data Form to capture information regarding infusion of (b)(4) prior to the collection of maternal specimens. Also, please provide the revised SOP that explains how this information will be factored into the DE determination.
   iii. Donor Eligibility SOP (CB37.0023.3) addressing: 1) DE determination and the proper designation of ineligible units prior to the release of cord units to the search inventory (we

understand that this will be completed by August 1, 2011), 2) DE criteria for licensed units.

7. In your sponsor letter to the questions discussed at the teleconference on 4/11/11, you described the process that is performed at the time of placenta retrieval, for donor identification and labeling in multiple birth settings. However, those details are not included in the Collection of Cord Blood SOP (CB37.0001.1). Current version of the SOP provides labeling instructions for single births only. Please provide the revised SOP.

8. Please provide clarification regarding the documentation of maternal information for maintaining linkage between the birth mother and the cord blood unit. According to the collection and maternal consent SOPs (CB37.0001.1, step 8.4.2 and CB37.0002.1, step 5.8.1), mother's name, medical record number and address is documented on the last page of the Data Form; however, the blank and the completed forms that you have submitted do not include a designated section for documentation of mother's information.

9. The quarantine procedure that you described in your response to the FDA letter dated 3/9/11, is not sufficient to prevent improper release of units prior to completion of the donor eligibility. Quarantine designation may be accomplished by various methods including automated designation, physical separation or other methods. Please provide additional information regarding your revised procedure.

LOT RELEASE TESTING

10. Please submit validation data for infectious disease testing performed. We note that the test kits are licensed or cleared, however, you should show at a minimum that the kits work the way they are supposed to in your hands (with various operators). In addition, please describe the samples used for NAT testing for HIV and HCV.
11. We note that you retest (b)(4) Cord Blood unit for HLA type before it is shipped. Data from these re-testings could provide evidence that the test method is reliable and accurate. Please submit data summarizing the frequency the HLA re-testing does not match the original HLA test. Please include a description of the course of action that was taken to resolve the discrepancy.

Flow Cytometry Comments

Instruments for analysis

12. You currently use (b)(4) flow cytometers for CB analysis. Section 2.2 of your BLA states that equivalent instruments could be used but criteria to establish "equivalency" were not submitted. If you want to use different instruments, you will need to submit to FDA a plan for establishing equivalency for review and approval. Also, you will need to submit data to support this change and await FDA approval before this change can be implemented (see comment on Flow Cytometer New Instrument Validation, #8 below)

Flow cytometry SOPs (SOP 27.0090)

13. Your SOP 27.0090 for analysis of cell samples by flow cytometry includes several types of samples that are not the intended cord-blood product. Please submit a revised SOP that is designed solely for the characterization of your intended clinical cord-blood product.

Sample quality and age

14. Section 6.4.2.2 of your SOP 27.0090 for analysis of cell samples by flow cytometry lists several sample age or quality attributes that may result in contacting the submitter of the sample and the need for supervisory review and sign off. Your revised SOP needs to stipulate that any samples that do not meet acceptance criteria will not be further processed for clinical use under the license.

(b)(4)

15. (b)(4)

Sample preparation

16. 6.4.4.1 instructs the analysts to add (b)(4) CD45/CD34 (b)(4) antibody into each sample tube. The reagents listed in Table 1, in Section 4.5.2 refer to antibodies supplied by (b)(4) either singly or in (b)(4) Please submit data to validate that single antibodies or pre-supplied mixtures both result in comparable assay performance. If such a demonstration is suitable, the SOP needs to include procedures for (b)(4) antibodies.

Flow cytometry analysis

17. 6.5.1 refers to several SOPs for instrument quality control and maintenance. These need to be updated to the most current versions of these SOPs. Please update the references to SOPs in your revised flow cytometry SOP.

18. 6.5.3 instructs the analyst to use the current CD45/CD34 acquisition template and further states that any changes to the template must be documented, approved by the laboratory director and filed in the laboratory. Please note that any changes to template should be subject to QA/QC review. In addition, the process for template generation and qualification of each revised template needs to be documented and supported with validation data.

Flow Cytometry Validation studies

19. Since accuracy could depend on instrument, set-up, and compensation, this test should be repeated 3 times with different lots of standards, different operators, different machines, and at different times. The different machines should be the (b)(4) that you are currently using.

   i. Since precision could depend on instrument, set-up, and compensation, this test should be repeated 3 times with the standard preparation and different product lots, different operators, different machines (b)(4) currently in use), and at different times.

   ii. Since linearity could depend on instrument, set-up, and compensation, this test should be repeated 3 times with different standard preparations, different operators, different machines ((b)(4) currently in use), and at different times.

   iii. Regarding the (b)(4) studies performed in 2008, more information is needed regarding the number of times this test was done, if there were different lots involved, and if there were different operators involved.

Flow Cytometer New Instrument Validation

20. Regarding new instrument validation, please note that new instruments should be qualified based on accuracy, precision, and linearity tests using the modifications to these assays described above, in addition to the analysis of (b)(4)

General comment on the flow cytometry assay

21. The descriptions of the flow assay lack any mention of positive and negative assay controls including isotype controls and positive and negative cell controls. These should be included in each assay to insure acceptable analytical performance.

STERILITY

Sections 4.1.3.1.2 and SOP CB40.0006.1 – Sterility Assay Protocol for Lot Release

22. We note that you have mentioned two ranges of incubation temperatures for your sterility assay: (b)(4) (under section 4.1.3.1.2) and (b)(4) (under SOP CB40.0006.1). Please clarify which one will be used for testing the sterility of your product.

23. Please provide representative (b)(4) for the following using your (b)(4)

i.
ii
ii
iv
v

(b)(4)

24. (b)(4)

25 (b)(4)

26 (b)(4)

27 (b)(4)

(b)(4)

28

instru

i. (b)(4)

ii.

1. It appears that you will be testing (b)(4) cord blood samples at a time for sterility. What is the maximum storage time for the respective plasma bags? How are you going to store them before the sterility test?

Section 4.3.2.1 and NCBP-VAL-10-003 – Sterility Assay Method Validation, Phase I study

30. We note that during this phase of study samples were shipped from NCBP to a Contract Laboratory at the (b)(4) and a Microbiology Laboratory at the (b)(4) (b)(4). Using a table please indicate the conditions, monitoring criteria and average duration of all respective shipments.

31. Table 5 (Section 4.3.2.1.9):
    i. Please indicate the actual absolute number of CFUs for each challenge strain used to inoculate the media.
    ii. Please explain the difference between NA*4 and NA*5 in Table 5.

32. The (b)(4) methods recommend a (b)(4) incubation temperature for molds as many of them would not grow at (b)(4) please clarify why this temperature is not used with (b)(4)

33. Please submit a list of microorganisms that you have isolated to date from your facilities and the cord blood units using your (b)(4) machines.

(b)(4)

35.

(b)(4)

36.

(b)(4)

37. We note that during this phase of study samples are shipped from NCBP to a Contract Laboratory at (b)(4) Using a table please indicate the conditions, monitoring criteria and average duration of all respective shipments.

38. Please describe how you have assessed the ruggedness and robustness of your proposed test method during the assay validation.

Thanks,
Terrolyn

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