Outstanding Review Issues Email, August 6, 2012 - Ducord

Date: August 6, 2012
To: Duke University School of Medicine
From: FDA: Denise Gavin, Mark Davidson,
RE: BLA 125407 Outstanding review issues
As part of our ongoing review of the original submission and subsequent amendments for BLA 125407 (Duke University School of Medicine) we have the following items that need additional clarification or revision. Due to the time sensitive nature of the review process, we respectfully request that you please respond to these items by Thursday August 9, 2012.
We would like to schedule a follow up phone call for Friday August 10, 2012 between 1-3 pm (2-3 pm preferred) to discuss outstanding items if necessary.

A. DE/Collection:

1. Please submit the final version of the draft SOP CCBB-LAB-017 that you emailed on 7/31/12.
    a. Related: Section 3.2.S.2.4 Control of Critical Steps states that cord blood units arriving from a remote collection site are accompanied by an electronic data logger (EDL) in the -------(b)(4)-------- shipper. ……. Data for all shipments are downloaded and if a temperature is out of range, a deviation is created. Please clarify narratives to indicate if the unit is banked or discarded.
2. Please submit the revised Kit Program Cord Blood Receipt SOP CCBB-COL-016. Similar to the above SOP, you need to specify whether units received from the **non-fixed sites** that don't meet the temp range are banked or discarded.
3. In email dated 7/17/12, you submitted draft CCBB COL-007 FRM2 which included detailed instructions for review of donor's medical and physical examination records. Please confirm that this form will be used for all fixed collection sites and submit the finalized form.
    a. Please submit the revised corresponding form for the Kit Program (CCBB COL-016 FRM2).
4. In response letter dated 5/31/12, you stated that donors that have positive screen results for HBc antibody, HTLV I/II and syphilis are not released to the search inventory regardless of the confirmatory tests. You submitted revised SOPs CCBB-LAB-020 and CCBB-LAB-002 that includes the correct info. But SOP CCBB-LAB-018, step 8.1.5, states that if "**the cord blood plasma is confirmed negative, the cord blood unit will proceed through normal banking procedure**". Please submit the revised SOP CCBB-LAB-018.
5. We suggest that you make the following revisions to the Cord Blood Unit Specifications form (CCBB-DIST-002 FRM2):
    a. For donor screening sections, please add a row for Clinical and Physical Evidence for Relevant Communicable Disease Agents or Diseases (RCDADs).

i. Please add the same criteria to the Exclusion and Quarantine Release Form (CCBB-QA-045 FRM1). On both forms, you have only listed the criteria/specifications related to the Family and Medical risk questionnaires and the Infectious Disease Test results.

b. Add final DE determination: Eligible, Ineligible or Incomplete DE (only units from eligible donors will be qualified for licensure).

6. Please clarify if the Carolinas Medical Center (#61) collection site has been brought on line? Please provide the abbreviation used for this site in the data tables.

B. Process Validation:

1. LAB-017: Under Materials, what is the role of '-------(b)(4)-------- Label set' in this BLA? Please delete references to '----(b)(4)----' in the BLA.
2. LAB-022: Please clarify where CBUs are 'discarded' versus 'excluded from banking', are the two the same?
   a. It is clear that CBUs with post-(b)(4) of (b)(4) are discarded, but it is not clear for pre-(b)(4) counts. For example, 4.9 states that samples with pre- or post-(b)(4) count of (b)(4) are discarded, but in 8.4.13.3 units are excluded from banking
   b. Same issue applies to -(b)(4)- counts of ----(b)(4)----
   c. Please remove reference to -(b)(4)- processing in 8.5.8.8.
3. LAB-022: Is the volume for **all** processed HPC-Cs -(b)(4)- as indicated in 8.7.4.4? The actual volume for each processed HPC-C in the range of ----------(b)(4)--------- should be provided in the (b)(4) report. Please comment.
4. LAB-022: A constant volume of (b)(4) (Total Volume) is used to calculate the TNCC for all processed HPC-Cs, but the volumes may vary for each unit (8.8.18.7). Please comment.
5. LAB-022: **----(b)(4)-----** is still referred to in 8.7.4.5.2. Please delete and state the disposition of these units.
6. There is a discrepancy between LAB-022 and LAB-024, please clarify: Post processing total volume range is reported in LAB-022 (8.7.5.2) as ------(b)(4)--------, however, it is reported in LAB-024 on page 1 (2.2.1) as -----(b)(4)-----.
7. LAB-024: Please clarify the version of -----(b)(4)------ kit used (----------(b)(4)---------- ...).
   2. Table S.6-1 Summary Container Closure Systems also indicates that ---(b)(4)- is used. Please make sure table is consistent with processing SOPs.
8. LAB-024: Please clarify the disposition of HPC-Cs that do not reach ---(b)(4)----; it is clear for HPC-C with freezing curve out of range.

C. Thawing/Wash Procedure:

1. **Procedure:** On page 25 of 29, section 2.10.d of CCBB DIST-028 it states to label the infusion bag with ISBT 128, however, you have been referring to the infusion bag as the bag containing cell suspension #1, is this bag not labeled early in the wash process or should the instruction be to label the transfer bag…please clarify.
   a. When are samples removed for post-thaw testing at the transplant centers?
2. **Validation:** Please clarify when samples were obtained for testing for the Thaw/wash validation study that was performed on (b)(4) units following process validation. It was not clear if samples were removed before or after the wash process.

D. Sterility: nothing at this time.

E. Viable CD34+ Assay Validation:

1. According to the validation studies, the range of the (b)(4) assay in your lab is reported as --(b)(4)-- CD34+ cells/ul, how does this range compare to most of your measured values for CBU samples? In another word, will most of the measurements from CB samples fall within this range? If not (either below (b)(4) or over (b)(4) CD34+cells/ul), what do you routinely do? How often do you see out of range samples? Do you plan to further validate your assay to lower the low end of limit of detection (LOD), or increase the upper end of LOD?
2. According to the additional information submitted on 7/23/2012, ----(b)(4)---- is not used regularly in the Duke Stem Cell Lab. Therefore, the ------(b)(4)----- plot is not available for all the recent 3 months. We suggest that this instrument ----(b)(4)---- should be used regularly and maintained properly as well as subject to regular QC check. Please submit -----(b)(4)----- plot of this instrument for FDA review once more data is accumulated.
3. In the Figure below (submitted 7/23/2012), it seems ----(b)(4)--- was compared to ----(b)(4)----, do you have data where ---(b)(4)---- is compared with the other ----------(b)(4)----------?

(b)(4)

4. Please clarify when you plan to implement the (b)(4) assay in the Duke SC lab for use on a routine basis. Many associated documents still refer to --(b)(4)-- as the method used to measure viable CD34+ cells. Please comment.
5.

F. Lot Release Specifications:

1. Please clarify your specification for TNCC in the BLA documents.
    a. In some places (i.e. LAB-022 CBU Processing and [FRM1] and LAB-024 CBU Cryopreservation) you state that if TNC count is <9x10e8 then the unit should be disposed according to *CBU Disposition* (CCBB-LAB-005 and LAB-005 FRM1), which indicates that <9x10e8 cells is reason for disposition.
    b. LAB-022 Processing FRM1 states to STOP HERE when post (b)(4) TNCC is <9x10e8 cells.
    c. However, *CBU Specification Form* (DIST-002 FRM2) indicates that units between (b)(4)< 9x10e8 cells may be released for transplant under IND. It is unclear how a unit can be release under IND if it was disposed of during processing. Please comment.
    d. Do you have different specifications for TNCC for BLA vs IND? It was our understanding that all CCBB units must have ≥9x10e8 cells.
2. You have different specifications listed for viability (CBU processing, viability SOP, and DIST-002 FRM2) depending on the origin of the collected unit. This is confusing, please revise form.
    a. And as we suggest below, references to CORD:USE should be removed from documents associated with the license for Ducord.
3. Please clarify specification for (b)(4) listed in CCBB-DIST-002 FRM2. The specification is listed as (b)(4) and (b)(4), with (b)(4) exclusion on FRM2 CCBB-DIST-002.

4. Please provide the CLIA certification number for the New England Newborn Screening Program (305 South Street Jamaica Plain, MA 02130-3597) that performs hemoglobinapathy testing. And a brief description of how results are obtained from the NENSP.

G. Stability

1. Protocol:
    1. Please clarify when samples are obtained post thaw for testing.
    2. Please clarify the percentage of units that come from CCBB and are transplanted at Duke that have a TNCC of --(b)(4)--.
    3. Please clarify why you will use CORD:USE units to determine ongoing stability and to increase expiry date for Ducord. CORD:USE units have different specifications and are not part of this BLA.
2. Data: Please provide data and data summary report to support expiration date.
3. Expiration date: see 2.
4. Please clarify if 10%DMSO/1%Dextran has always been the cryoprotectant used at CCBB. If not, please specify when use of DMSO/Dextran was implemented.

H. Other

1. Please clarify the relationship, if any, between NMDP Cordlink, --(b)(4)-- and NMDP Traxis and --(b)(4)-- database management.
2. Please clarify how the "local web-based CCBB search registry" operates? Is this registry just for Duke transplants? Who can search this registry?
    a. CCBB-DIST-025 Overview of Selection, Release, and Transport to Transplant Facilities states that qualified units are placed in the **local, web-based Carolinas Cord Blood Bank (CCBB) search registry,** which is managed by The -(b)(4)- Corporation and can be accessed by transplant coordinator searching for potential donors for their patients.
        i. The SOP states that CCBB units are also listed in the registry of the National Marrow Donor Program (NMDP) and are available for search through the NMDP web-based system Traxis.
        ii. However, all subsequent CCBB procedures and controls for searching, matching and ordering processes only mention NMDP procedures (e.g. SOP CCBB-DIST-026 Ordering and Release of Cord Blood Unit for Transplant doesn't discuss how units are handled following direct selection from the local CCBB registry).
3. Please clarify what happens when a unit is "medically deferred" from the bank. CCBB-DIST-025 states that if during a search of the NMDP database it is determined that a selected donor in the database is the same as the patient, that the HPC-Cord blood is permanently medically deferred at the bank.
4. Please clarify storage temperature for Ducord. Storage temperature is listed as --(b)(4)-- in some places in the BLA and $\leq$-150C in others.
5. SOP CCBB COL-009 page 1 of 6 states that up to (b)(4) CBUs can be stored in the CCBB transport containers for a maximum transport time of --(b)(4)--. Local transport shippers have been validated for a max of --(b)(4)--. Please revise.
    a. Please make sure this is consistent with other related SOPs, forms, narratives.

b. In addition, if the storage and/or shipping process were changed due to 2nd validation study (e.g. +/- stabilizing packs, (b)(4)) please make sure changes are reflected in the related SOPs.

5. CCBB-DIST-002 FRM2 (ver 08 effective 27 Jul 2012):
    i. See above for additional DE/Collection info to be added to form
    ii. Under Confirmatory Typing:
        1. The --(b)(4)-- assays are listed as For Information only, but there is still a pass/fail designation, making it unclear if units that fail these specifications will be released to the transplant center. Please clarify what decisions are being made based on these tests.
    iii. Under Laboratory Data:
        1. Units are released based on CD34+ counts ("Test Method: ---------(b)(4)----------"). Ducord units will be released based on (b)(4) assay. Please revise.
        2. Please clarify if the specification for (b)(4). DIST-002 FRM2 indicates that the Specification for (b)(4) is (b)(4), but other places the specification is listed as (b)(4) (e.g. Table S.4-1, Table 5-1 Process Validation Specifications).
            i. As discussed above, DIST-002 FRM2 indicates that units between (b)(4)<9x10e8 can be released for transplant under IND, however, your processing SOPs indicated that units with <9x10e8 cells should be discarded.
        3. Under viability you are including CORD:USE or LifeShare units, which have different specifications from the CCBB units. It is not clear how Cord:USE vs CCBB units are distinguished during receipt, processing, storage or distribution, yet there are different acceptance criteria, which could be misunderstood.
            i. How does the technician performing viability during processing know if a unit is to be discarded for viability below (b)(4) or if it is a CORD:USE unit and 85% viability is sufficient?
6. EXCLUSION AND QUARANTINE RELEASE FORM CCBB-QA-045 FRM1 also contains references to Cord:use or LifeShare.
7. According to Amendment 008 (May 31, 2012) the acceptance criteria for collection volume is listed as -(b)(4)- in Module 2, section 2.3.S.2.4 Table S. 2-3. This section does not reflect that -(b)(4)- must be collected from Caucasian donors.

I. Contract manufacturing by CCBB:

1. CCBB contract manufacturing should be clearly separated from Ducord manufacturing. Separate forms should be generated for contract manufacturing documentation. It seems most of these references have been removed from SOPs; however, some CORD:USE references remain in the Viability SOP, CBU processing and CCBB-LAB-022 FRM1, etc.
    a. There may not be a need for separate SOPs as long as procedures are the same, but there should be different associated batch record forms especially given that there are differences in specifications (i.e. viability).
    b. There should be clear distinction between CCBB licensed units and CORD:USE. Since the Form2 is for distribution of CCBB Ducord or CCBB IND

units and there is no final release designation box for CORD:USE units, please remove these references.

c. This needs to be clarified on all related documents and
d. Reference to CORD:USE should be removed from all Ducord related documents.