Teleconference minutes

Duke University School of Medicine, Carolina Cord Blood Bank:
Bruce Burnett, Becky Dunham, Joanne Kurtzberg, Anna Valverde

FDA: Joydeep Ghosh, Nancy Waites, Loan Nguyen, Mercy Quagraine, Cheng-Hong Wei, Denise Gavin, Mark Davidson, Keith Wonnacott, Ronald Chamrin

Re: Outstanding review items for BLA SN125407
When: July 17, 2012
Time: 4-5 pm

A. Sterility validation update: Ghosh:

a. Please confirm in writing that the sponsor will use cord blood from donor mothers on perinatal prophylactic antibiotics.

i. Please include the percentage of mothers who are on this type of antibiotic prophylaxis, and

ii. Justify why they think it will be safe even though it might interfere with the sterility assay.

b. Timing for the justification/rationale submission.

B. Local shipping questions: Waites/Gavin:

a. Clarify max time frame is --------(b)(4)--------- dispose? Duke: yes.

i. FDA suggested Duke monitor the temperature in the transport vehicle to ensure that temp remains within the range used for validation study.

1. DUKE: No plans currently, drivers don't make long stops with units in vehicles. Vehicles are air conditioned. Will consider the use of data loggers in transport vehicles and get back to us with their decision.

b. Process for revalidation, bringing new transporters on-line, etc

i. DUKE: no revalidation since coolers only last about (b)(4) and are replaced…new coolers validated.

c. Why not have data loggers on local transport as agreed upon at inspection?

i. DUKE: Problems with consistent operation of loggers.

C. Proprietary Name: Nguyen and Davidson:

a. Inform sponsor that the proprietary name on package insert and container label should be DUCORD (all caps) and in box lettering rather than DuCord (mixed case letter or tallman lettering).

b. Presentation of the product proprietary name on product logos or other promotional materials can be of the sponsor choosing. APLB can provide advisory comments when requested, but the FDA does not approve logos or promotional materials.

c. Remainder that all communication in the future will reference your HPC-, Cord Blood product as DUCORD as the proprietary name.

D. Process validation issues: Quagraine:

Validation Protocol:

1. Please provide transport time duration for all CBUs used in validation.

2. Please explain why the conditions for shipping collected CBUs described in Protocol as (b)(4), is modified in the Validation report to --(b)(4)--.

3. FYI only: Criteria described in Tables 6-1 of *validation protocol* and 5-3 of *validation report* are not acceptable. Historical data should be used to set specification for attributes. For example, if based on analysis of historical CD34+ cell data, the recovery is 80 ± 5%, you can set an acceptance of 75% for that attribute. Historical data should not be used in the way you describe here; we can meet this specification (b)(4) of the time because we have met this (b)(4) of the time.

4. Please clarify the column headings in Table 3 of *validation report*; pre-cryopreservation values vs post-thaw values.

5. Please explain the low CD34 recoveries (around (b)(4)), but high post-thaw viabilities of (b)(4).

6. Please provide information on post thaw CD34+ cell viability (and/or (b)(4) viability information)

7. Please provide the raw data on the actual masses measured for the volume check and the volumes measured for the two units used in the validation.

8. Please note that the reagent list does not include DMSO/Dextran40.

9. How is the 48 hour window from collection to completion of processing controlled/documented so you do not go beyond this time duration?

10. Collected cord blood volume was specified at (b)(4) minimum in order to be processed, in previous submissions. However, information in validation protocol and report introduces two new volume specification for minority donors -(b)(4)-, and Caucasian donors ((b)(4)). Clarify. Please revise/update all affected documents to reflect this.

11. Please include an interpretation of results section in report to explain modifications and deviations.

Revised SOPs:
LAB-022

1. Please clarify your policy on --(b)(4)-- counts of --(b)(4)-- and pre-processing (b)(4) measure of (b)(4). After platelet slide review and dilution and re-assay, are such units processed or discarded?

2. Calculation in section 8.4.11.4 and sections 8.8.1.8.7 may need revision; is it times or divide by (b)(4)?

3. Section 8.6.5.1: provide the volume range for (b)(4) processing (---(b)(4)---------). Unclear when the volume is quoted as ----(b)(4)---- with Hespan.

4. Clarify policy in situations when supervisor is notified. For example,
   a. ----------(b)(4)----------,
   b. ----------(b)(4)----------,
   c. ----------(b)(4)----------,
   d. ----------(b)(4)----------,
   e. ----------(b)(4)----------,
   f. ----------(b)(4)----------,

5. Clarify policy on (b)(4) TNC recovery post processing: it is unclear what happens when TNC is >9 x 10^8 cells but TNC recovery is (b)(4)

6. FRM1:
   a. Under 'Post Processing Counts', steps 2 and 3 may need be revised.
   b. Delete references to ----(b)(4)-----

7. Reminder: please revise the SOP to eliminate referenced to ----(b)(4)-----.

LAB-024

8. Under equipment, delete reference to --------(b)(4)------- for --(b)(4)---- processing

9. Please specify Priming volume of DMSO/Dextran for tubing and volume of DMSO/Dextran added to HPC-C. This information does not appear in SOP.

E. Stability plan: Gavin/Wonnacott:

a. It was not clear from submitted information if the "potency assays" (% (b)(4) viability, ------(b)(4)-------, (b)(4)), have been validated, please clarify

i. Duke: We have not validated the "potency assays." The sponsor emphasized that these assays are superior indicators of stability and product quality. They plan to validate at later date.

ii. Duke will work to validate potency assays in a timely manner, and remove reference to these assays in stability protocol for now and submit a supplement to BLA once "potency" assays are validated. Please see related item below regarding product release statements.

iii. FDA: we can look at a validation proposal and help you get this done in a timely manner. Alternatively you can update the BLA to reflect this discussion as outlined below (F.c.).

b. Stability acceptance criteria. (--------(b)(4)---------) – is not acceptable.

i. Please provide rationale for specification.

ii. Need specific criteria that must be met to support ongoing stability, specification should be modified.

iii. Outliers can be investigated to support ongoing stability if no obvious trends are emerging.

F. Product Release: Gavin:

a. The following discussion points were discussed in the context of the stability plan, please let me know if you have additional questions.

b. QC decisions for product release can not be based on assays that have not been validated as this does not meet CGMP requirements.

c. Thus, in addition to modifying the stability protocol (see above), you also need to modify your release specifications outlined in Section 3.2.P.5.1 or submit validation data for "potency assays".

i. Product release is based on meeting specifications for -(b)(4)- viability, -----(b)(4)------ cells and (b)(4), which is tested on a sample from the attached segment. And, the BLA contains the statement that "Any unit failing to meet these specifications remains with the CCBB and is not released to a transplant center".

ii. Additional data is required to support the use of the "potency assays" to limit release of your product to a transplant center (i.e. these assays need to be validated).

iii. It should be noted that you also must establish that the segment data is representative of the unit as a whole. Previous discussion indicated there were differences between the segment and the unit related to quality control parameters. Please comment.

a. If you choose not to validate the "potency assays" at this time, you must remove the above product release constraints from the BLA. You may submit a supplement to the BLA stipulating HPC-C release specifications based on these potency assays after the "potency assays" have been validated.

i. To proceed with the BLA review at this time, the BLA should be modified to state that these assays will be performed for information only and that once these assays are validated they may be used for product release.

b. As we requested previously on May 15 2012, please provide ----(b)(4)---- plot, instrument QC record for the ----(b)(4)---- in the last 3 months, and instrument cross-check results (cross check between ----(b)(4)---- and ----------(b)(4)----------)

G. Please submit updated BLA according to our discussion within one week (by 7-26-12).

H. The following were not discussed during t-con due to time constraints but are relevant to this discussion, please let us know if you have additional questions:

i. Validation of viable CD34+ cells was performed at the SCL. Validation of % viability assay by ----(b)(4)---- was performed at

CCBB post process, was the SCL involved in the validation? Does the SCL use the same SOP (CCBB-LAB-025) for the validated viability assay used at CCBB? Please clarify.

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ii. The analytical assays and acceptance criteria discussed on 3-2-12, during the inspection for measuring potency are not consistent with what was proposed in Am8 received on May 31, 2012. For example, the specification for (b)(4) (at SCL) was (b)(4) recovery; %TNCC recovery was listed as (b)(4). Engraftment data was listed as 'For information only." Please comment.

E. Discussions at that time ruled out including viable ----------(b)(4)---------- preformed on the segment because data was not currently available to establish that the segment was representative of the CBU), and because the assays had not been validated. These two items need to be addressed for the "potency" tests performed on the segment to be used to establish stability and expiry date (and product release).

F. There was also no discussion of generating scores of (b)(4) or (b)(4) as acceptance criteria.

iii. There are several errors in the text of the Stability summary, which made it difficult to follow the conclusions made. These include but are not limited to the following:

1. For example, pg 16, Figure 19A is a correlation between (b)(4) and -(b)(4)- but text indicates it is a correlation between engraftment and --(b)(4)--.

2. Conclusions are made based on ----(b)(4)---- but the variable presented in Fig 19A is absolute number of viable --(b)(4)-- cells.

3. Figure 19B is a correlation between (b)(4) and CD34+ but text indicates it demonstrates a lack of correlation between CD34 and engraftment.

4. You also made a statement that "only 33% of the units with ----(b)(4)---- engraft, but there doesn't appear to be any units in Fig 20A at (b)(4).

5. On pg 17 you conclude that there is no correlation between time in storage and --(b)(4)--, viable CD34 cells or (b)(4) (Ref Fig 20 A, B, C) but data seems to be related to Fig 21

A, B,C and Fig 22 A, B, C). However, Fig 21 and Fig 22 do not include time in storage data to make that conclusion; in fact they appear to contain the same data.

6. Please clarify the Stability summary.