# Discussion of Responses Telecon, January 6, 2012 - Ducord

Minutes from Friday January 6, 2012 T-con with the sponsor:
Introductions:
FDA: Mark Davidson, Safe Karandish, Joy Ghosh, Denise Gavin, Cheng-Hong Wei, Mercy Quagraine
Duke Attendees: Joanne Kurtzberg, MD- Medical Director, CCBB, Bruce Burnett, PhD- Director, Regulatory Affairs, Amanda Parrish, PhD- Regulatory Affairs Scientist
Rebecca Durham- Project Leader, ----------(b)(6)----------

RE: Discussion of responses to the Filing letter and ongoing review concerns for BLA 125407, Duke University School of Medicine

1.The need for method and process validation studies that meet GMP requirements was discussed.

2. Method validation plans (responses to Q#2) submitted in response to Q2 were not adequate to evaluate validation protocols.

b. Additional information submitted on Jan 6, 12012 has not yet been reviewed.
c. The sponsor was informed that they will must conduct method validation studies that will meet GMP requirements (21 CFR 211.165(e): accuracy, sensitivity, specificity, and reproducible. And 21 CFR 211.194(a): documentation) for methods used for lot release (into depository) and to establish expiration date (21 CFR 211.137(a) based on stability studies (21 CFR211.166).
d. We recommend that assay validation protocols be reviewed and approved prior to initiation.
e. We recommended that method validation protocols including detailed descriptions of critical assay characteristics you intend to assess for review. We recommend that you evaluate a sufficient number of samples and replicates to ensure statistical evaluation of data, and that you evaluate potential sources of variability including but not limited to:
    (1) Type and number of different machines/equipment used,
    (2) Number/type of samples,
    (3) Operators/days,
    (4) Reagent sources,
    (5) Controls
f. Please describe how the assessments will be conducted, what type of statistical evaluations will be used, how you will justify robustness and how results will be reported.
g. Specifically for -----(b)(4)--------
    1. Validation studies: accuracy, precision, linearity, limits of detection for viable CD34 as potency assay, CD34 and (b)(4) as stability assay;

2. Comparability: multiple operators; different ---(b)(4)----;
3. Instrument set-up for CD34 enumeration and viability assays: (b)(4) template, representative data analysis, sample dot plot.
4. ---(b)(4)--- instrument quality control and maintenance: daily ---(b)(4)---, maintenance procedure;
5. Training and competency of ------(b)(4)----- operators: accreditation, training;
6. Reagent qualification program: new lot of ----------(b)(4)----------
7. -----(b)(4)------ instrument comparabilities studies, new -----(b)(4)------- instrument validation program

3. We discussed our concerns about the proposed stability protocol revision (described in responses to question 3).
    a. It does not appear as though Duke has conducted or intends to conduct a real time stability study as required for licensure (21 CFR 211.166). We informed the sponsor that they must assess stability indicating quality parameters using validated methods in a prospective stability study to establish expiration date and to extend expiration date to meet GMP requirements for licensed products. Please refer to section VII.B.14.e of the Cord Blood Guidance (October 2009) for additional information.
    b. We requested that they submit a stability protocol outlining which validated methods will be used, preset acceptance criteria, sampling times, number of samples, considerations for different manufacturing processes used, and any other relevant information.
    c. Please note that your specification for nucleated cell viability post-thaw should be (b)(4) viability. It is not clear if the (b)(4) recovery specification meets this standard. Please clarify this specification in your stability and thawing validation study protocols.

5. There was a discussion of how many units to use. We suggested that they submit a proposal considering our past advice.
    a. There was a discussion of how the data submitted for released units is generally supportive of product stability, but not sufficient, and that data may not be representative of the inventory (i.e. units released for transplant are pre-selected for potency).
    b. In addition, the use of average values can be biased, and without reviewing individual unit data we are reluctant to conclude all units are comparable.

    (1) Real values for set number of units from set time points should be submitted, not just average values. Averages don't allow for examination of outliers

    (2) Supportive data may be submitted: clinical and literature.

6. Additional Information:

. Mark Davidson (RPM) will schedule a separate telecon later to discuss Duke's manufacturing process.

a. Regarding the Process Validation: It was noted that what DUKE has submitted is more of a comparability study for the -(b)(4)- versus the (b)(4) procedures and not a process validation study. This information had been submitted in the pre-BLA package and the sponsor was notified at the time that the data was inadequate. The following was also relayed to the sponsor:
b. Process validation should have a validation protocol/plan, which analyzes critical process parameters, has pre-set acceptance criteria and analyzes consecutive process operations. The protocol should be approved by the quality unit and may be submitted to the FDA for comment before execution. In addition to the protocol, the sponsor will submit a validation report which describes what was done, the results obtained, the interpretation of the results and conclusions of the study.
c. Regarding the use of consecutive CBUs for the study, it was recommended that the use of CBUs processed within a set timeframe for evaluating the entire process from collection to cryopreservation was acceptable. Alternatively, they could break up the process into steps; however, they would like to perform the validation. The sponsor indicated that a validation protocol would be submitted for comment.
d. The information submitted as validation for the collection procedure can be used as supporting data; however we need a prospective validation using current SOPs. The validation plan should include pre-defined acceptance criteria and the number of products to be evaluated (see item d regarding the option for a comprehensive validation plan that would include collection).
e. BLA states that for collections at non-fixed sites, there is an agreement with the birth mothers but there is no mention of any agreement or arrangement with the collectors. Sponsor explained that the physician/delivery nurses signing the training document also agree to perform the collection according to the bank's SOPs. Sponsor was asked to submit this information in writing.
f. We discussed that the responses to the following items in the filing letter would not meet the regulatory requirements:

(1) Item #1(c)- Review of birth mother's medical and physical examination records: It was explained that this review is required for screening the donors for risks of Cads. Completing donor questionnaire would not be sufficient. It was suggested that for collections at non-fixed sites, cord bank may either request a copy of the record or ask the individuals responsible for the collection to provide the needed information for completing the donor screening. Sponsor was asked to submit updated SOPs.

(2) Item # 7- Assessment of birth mothers for the possibility of plasma dilution- We discussed that the sponsor must have procedures in place for determining whether or not the birth

> mother has received transfusion or other IV infusions (crystalloids) prior to obtaining the specimens for infectious disease testing. Sponsor explained that donors receiving blood transfusion are not accepted. They will review the regulations to address the infusion of crystalloids. FDA agreed to review the draft procedures.

The discussion concluded with Duke agreeing to submit requested method, process and stability protocols. FDA agreed to have a follow up conversation next week to discuss process related issues.
Note: References to the 1271 regulations and the relevant sections of the DE guidance regarding the donor screening and plasma dilution were emailed to the sponsor on 1/6/12.