



Our STN: BL 125657/0

BLA FILING NOTIFICATION

August 22, 2017

MD Anderson Cord Blood Bank
Attention: Elizabeth Shpall, M.D.
1841 Old Spanish Trail
Houston, TX 77054

Dear Dr. Shpall:

This letter is in regard to your Biologics License Application (BLA) received on June 26, 2017, under section 351(a) of the Public Health Service (PHS) Act for Hematopoietic Progenitor Cells, Cord Blood (HPC-C).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Under 21 CFR 601.2(a), this application is considered filed today. The review classification for this application is **Standard**; the review goal date is June 26, 2018. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

While conducting our filing review, we identified the following potential review issues:

Chemistry, Manufacturing, and Controls:

Collection and Donor Eligibility

1. Regarding SOPs for in utero collection of cord blood units at remote collection sites you have submitted CBB S 016.013.001 but there is also a reference to CBB S 004.005.001 titled In-utero Cord Blood Collection Using (b) (4) (not submitted) in CBB S 016.010.001. Please clarify whether you have one or two SOPs for in-utero collection of cord blood units at remote collection sites. Please include the missing SOP if applicable.
2. We understand that the storage temperature for collected cord blood units at the hospitals and during transport to the cord blood bank is between 15-30°C (SOPs CBB S016.007.003, CBB S 016.004.002, CBB S 007.002.003, Policy CBB P 055.001.004, Figure 3.2.P.3.3-1, and 3.2.P.3.3.1.7) and the temperature is continuously monitored using a min/max thermometer. However, the summary sections of the BLA or the SOPs do not explain how out-of-range temperatures during storage and/or transport are handled and whether the affected units are accepted for banking.
3. We are unable to determine whether cord blood units from donors that test positive for anti-HBc are listed with the registry because of the following discrepancies:

- a. Tables 3.2.P.3.4-4 and 3.2.P.5.1-3 Registry Listing: All tests negative, except CMV
- b. Documents CBB P 055.001.004 (Step 4.5.3, Table 2), Cord Blood Bank Infectious Disease Testing and CBB I 085.020.003: units from donors with initial reactive anti-HBc result but non-reactive confirmatory test result or with negative HBV NAT result are acceptable and stored as “FDA ineligible”.

Please address the above and submit the revised documents.

4. We are not able to determine the criteria for licensed versus unlicensed units that you list with the registry. For example, for donor eligibility, CBB P 055.001.004 does not specify that only units from donors who have been determined to be “Eligible” based on the results of all screening and testing are qualified for licensure. Additionally, the CBB S 008.002.003 does not explain whether units from donors for whom donor eligibility has not been completed are stored and used under an IND.
5. CBB S 004.001.004 and CBB S 016.012.001 explain that maternal specimens should not be collected from birth mothers who have received a predefined volume of colloids and crystalloids. However, it is unclear how the assessment is made at local and remote collection sites. Please address the following:
 - a. According to CBB S 004.001.004, maternal specimens at local hospitals can be collected by CBB collectors or hospital staff. Please explain who is responsible for completing the Transfusioncalculation.xlsx referenced in this SOP.
 - b. According to CBB S 016.012.001, maternal specimens at remote hospitals can be collected by CB Assistants, labor and delivery staff, or phlebotomy team. Please clarify who is responsible for completing the Transfusioncalculation.xlsx referenced in this procedure. Additionally, please provide information about the training program for the above individuals.
 - c. Volume of infused colloid or crystalloid is not documented on the Maternal Blood Sample Collection form (CBB W 081.096.003).
 - d. On Cord Blood Donor Labor and Delivery Form (CBB W 0081.093.003), volume of infused blood products are documented but there is no section for documenting volume of infused crystalloids.

Please submit the revised SOPs, form and the calculation worksheet.

6. Table 3.2.P.5.2-2 does not include the donor screening assay that you use for testing birth mothers for *Treponema pallidum*. Please submit the assay information and associated FDA approval number (STN).

7. Please address the following regarding the infectious disease assays listed in Table 3.2.P.5.2-2:
- a. You have listed three assays for anti- HIV and two assays for HBsAg. Please clarify which assays are used for screening the birth mothers for the purpose of donor eligibility determination and explain the use of the additional assays.
 - b. You have listed two donor screening assays for the following infectious disease tests:
 - i. Anti-HTLV I/II: (b) (4) [REDACTED], identified as the confirmatory test.
 - ii. Anti-HCV: (b) (4) [REDACTED] identified as the confirmatory test.

Please note that if a donor tests positive or reactive with one donor screening assay, the donor must be considered ineligible regardless of the results of any additional tests. Please explain the reason for the use of the second screening assay for the above infectious diseases and how the results from these assays are factored into the final DE determination. Additionally, for (b) (4), you have provided the manufacturing facility license number instead of the STN for the assay, and for (b) (4) [REDACTED] assay, you have provided an STN that does not appear to be an FDA assigned number. Please provide the correct STNs for these two assays.

- c. We are not able to determine whether you are using a multiplex NAT assay for HIV, HCV and HBV or individual assays. In CBB S 006.002.001, section 8.5.8, you refer to (b) (4) combined nucleic acid test for HIV-1/HCV/HBV (NAT HIV/HCV/HBV)". However, on Table 3.2.P.5.2-2, you have listed 3 individual NAT assays from (b) (4) [REDACTED]. Additionally, the STN BL (b) (4) that you provided for HIV NAT does not appear to be the correct number.

Please address these issues and submit the revised documents.

8. Please provide the following documents for review:

CBB I 085.057 Cord blood unit check in (referenced in CBB S 007.004.005)
CBB I 085.058 Cord blood unit acceptance (referenced in CBB S 007.004.005)
CBB I 085.065 CBB MHQ/FMHQ versions – missing questions (referenced in CBB S 006.001.001)
CBB S 008.001 quality assurance review of cord blood units prior to distribution (referenced in CBB S 006.001.001)

CBB P 053.001 cord blood collection site and donor education (referenced in CBB S 004.004.002)

CBB P 054.001 communicable disease suitability (referenced in CBB S 008.002.003)

Processing

9. We are unclear about the difference between retention and reference samples as described in your submission. In accordance with 21 CFR 211.170, an appropriately identified reserve sample representative of each HPC Cord Blood unit must be retained. Please provide a complete description of sample(s) that are saved as retention(s). The description should include a complete list of these samples (if multiple samples are saved), the amounts stored, the containers used to store them, and the temperatures stored. Please be aware that the reserve samples should consist of at least twice the quantity necessary for all tests required to determine whether the HPC, Cord Blood meets its established specifications, except for sterility.
10. Please provide a certificate of analysis (COA) for the DMSO/Dextran 40 reagent used as cryopreservative in manufacturing

Collection Validation

11. We note that the cord blood units are shipped from local collection sites to the manufacturing site in a transport tote with calibrated min/max thermometer with stabilizing gel packs. It is unclear from the submitted materials what the actual shipping and handling times are, as well as whether the transport totes are capable of maintaining ambient temperature conditions while being shipped. Please submit data from validation studies that support the shipping times and transport temperature conditions from the collection sites to the manufacturing sites; data from mock shipments using stress conditions such as temperatures outside your set limits and the farthest collection site would be adequate
12. Please submit your SOP for management/replacement of thermometers and temperature data loggers used in transporting cord blood from the collection sites.

Product Testing

13. "Description of Manufacturing Process and Process Control" (3.2P.3.3-1 Table and 3.2P.3.3-11 Figure) as well as CBB V 013.041 described the sterility testing procedure that involves (b) (4) [REDACTED] This sampling volume is not considered to be sufficient for sensitive detection of sterility failure of the processed Cord Blood (CB). Testing by-products RBC from CB processing as the surrogate for sterility testing of the final CB product need to be conducted with at least (b) (4) [REDACTED] volume. Please note that (b) (4) [REDACTED] also specified the examined specimen volume should be (b) (4) [REDACTED] for an optimal testing result (Please refer to (b) (4) [REDACTED] Package Insert). Please

submit the revised sterility testing SOPs of (b) (4)

CBB V 013.041 described validation assay results of (b) (4) (each with documented (b) (4) without (Table 3) and with (b) (4) test samples (b) (4) (Table 4). Therefore, you are not required to perform a new validation study.

14. Please submit the revised sterility testing SOPs of (b) (4) CBB V 013.041 described validation assay results of (b) (4) (each with documented (b) (4) without (Table 3) and with (b) (4) test samples (b) (4) (Table 4). Therefore, you are not required to perform a new validation study.

15. Please provide CLIA certificate for (b) (4) contract testing laboratory that performs the confirmatory HLA typing.

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, Virginia Ocampo, at (301) 348-3949.

Sincerely,

Kimberly Benton, Ph.D.
Associate Director for Regulatory Management
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research