

DHT Review Memo- Response to CR Letter

Review Memo for: STN 125764/0.35

Applicant: StemCyte, Inc.

Date: March 15, 2024

Reviewer: Hanh M. Khuu, MD, OTP/OCTHT/DHT/HTRS

Concurrence: Ping He, MD, Staff Chief, OTP/OCTHT/DHT/HTRS

Scott Brubaker, Division Director, OTP/OCTHT/DHT

To: Saravanan Karumbayaram, PhD, OTP/OCTHT/DCT1/CTB1

Product: HPC, Cord Blood

Submission type: Biologics License Application (BLA)

Discipline(s) Reviewed: Review is limited to information about donor eligibility (DE) in 21 CFR part 1271 in response to Complete Response Letter issued on January 20, 2023.

Documents reviewed:

STN 125764/0.36-0.38 – relevant sections pertaining to DE and responses to CRs

SUMMARY:

This memo describes the review of the applicant's responses to the Complete Response (CR) Letter dated January 20, 2023.

In the original submission (125764/0.0), StemCyte, Inc. described their procedures for donor screening, donor testing and making a donor eligibility determination, and product tracking. Based on the information submitted, it was unclear whether the donor eligibility determination is completed in accordance with 21 CFR part 1271. Comments to the applicant were included in the CR Letter.

In this submission (125764/0.35), the applicant addressed the CR Letter comments as well as provided updated information related to DE, including new and revised standard operating procedures (SOPs) and forms.

StemCyte has contracts with (b) (4) hospitals in (b) (4) for the collection of cord blood units (CBUs) and maternal blood specimens. Manufacturing, including processing and storage of HPC, Cord Blood products are performed at the StemCyte, Inc. facility in Baldwin Park, California.

Birth mothers and infant donors are evaluated for relevant communicable disease agents or diseases (RCDADs). Donor screening includes a donor medical history interview and review of the relevant medical records. The donor medical history interview of the birth mother is performed using the NMDP Cord Blood Maternal Risk Questionnaire (NMDP F00316) and NMDP Family Medical History Questionnaire (NMDP F00323). Review of the relevant medical records of the birth mother and the infant donor is documented on three (3) different forms. These activities are performed by StemCyte trained staff or hospital personnel trained by StemCyte. Donor testing is performed on birth mother blood specimens collected within 7 days of the infant's delivery. Testing is performed at (b) (4) in (b) (4). The testing laboratory has a current CLIA certification and registration with the FDA. The donor eligibility determination is performed by the Medical Director of StemCyte.

StemCyte utilizes two (2) systems of barcodes for labeling and tracking: a sequence of numbers with barcodes at CBU collection and specimen collection for testing for RCDADs and the ISBT128 barcode labeling system after the CBU meets all criteria for further processing.

Please refer to DHT memo dated December 16, 2022, for a complete description and details of the donor eligibility process and product tracking.

Complete Response Letter Comment 1a: Regarding donor medical history interview in Section 3.2.S.2.2.1.1, you indicate that the medical history interview of the birth mother may be completed 30 days after the cord blood collection date. Please clarify

whether donor medical history questions are posed to the birth mother, such that the responses to the questions are relevant to the date of cord blood unit (CBU) collection.

Applicant's Response: StemCyte submitted a revised description of the donor screening process and procedure in which the birth mother's medical history interview will be performed within 7 days before or after cord blood collection date.

Reviewer comment:

BLA Section 3.2.S.2.2.1.1 Donor Screening and SOP 11.1.022-PU Review of Donor Records for Donor Eligibility Determination was revised: "the medical history interview of the birth mother is conducted within 7 days before or after cord blood collection. If the medical history interview is conducted more than 7 days before the collection, any changes in the medical history are obtained and documented at the time of [cord blood] collection on the Maternal Health History Update Form and reviewed by the medical director for acceptability."

The revised procedure is acceptable.

Complete Response Letter Comment 1b: With reference to the review of relevant medical records of the birth mother and infant donor, SOP 11.1.022-PU outlines the procedures for DE determination. Furthermore, SOP 12.1.003-PU outlines the procedures for review of medical records for, and clinical evidence of, Relevant Communicable Disease Agents or Diseases (RCDADs). However, these Standard Operating Procedures (SOPs) do not describe whether a cord blood donor is determined eligible if a "YES" response is documented for any item in Section B (pre-delivery / delivery events or complications and pregnancy history) and Section C (infant assessment) on the Collection and Delivery form (12.3.008-02-PU). Please revise the SOP to describe how each item with a "YES" response is evaluated when making a DE determination and submit the updated document.

Applicant's Response: StemCyte explained that SOP 11.1.013-PU provides individual screening criteria for each question asked of the birth mother on the NMDP questionnaires, which includes how to evaluate "YES" responses for questions related to the screening for RCDADs as well as heritable disease risk captured in the Family Medical History Questionnaire. In addition, StemCyte revised SOP 12.1.003-PU and SOP 12.1.009-PU to describe steps to be taken when the "YES" response is recorded.

Reviewer comment: SOP 11.1.013-PU addresses the donor medical history interview questionnaire. SOP 12.1.003-PU and 12.1.009-PU address review of the forms that document review of relevant medical records. Additional details below in response to comment 1c.

The revised SOPs are acceptable.

Complete Response Letter Comment 1c. The Collection and Delivery form (12.3.008-02-PU) includes the following statement: “maternal hospital medical records have been reviewed for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases including HIV, HBV, HCV, syphilis, HTLV, WNV, vaccinia, Zika virus, and human transmissible spongiform encephalopathy, including vCJD”. The same statement is included on the Maternal Health History Update form (12.3.017-PU) and the Maternal Blood Sample Collection and Medical Records Review form (12.3.017-01-PU). It is unclear how the person (healthcare provider or StemCyte staff) that completes this section is informed which risk factors, clinical evidence, or physical evidence of RCDADs they evaluate. Please submit an SOP or instructions that you provide to healthcare providers and StemCyte staff for review of this information.

Applicant’s response: Two (2) job aids were created “to assist the health historian and medical records reviewer in evaluating individual responses to questions and to aid in performing the medical records review for evidence of RCDADs.”

Job Aid 11.2.022-PU Donor Screening Tool for RCDADs

Job Aid 11.2.022-01-PU Physical Examination Supplemental

Reviewer comment: Though StemCyte created the new job aids, these job aids were not included in the instructions for staff to refer to when performing the medical records review. In response to an information request (Amendment 37), the applicant revised the form instructions provided on the reverse side of the relevant forms (collection and delivery form, maternal blood sample collection and medical records review form, and maternal health history update form) to include the job aids.

The new procedures and revised forms are acceptable.

Complete Response Letter Comment 1d:

With reference to the information provided in BLA section 3.2.S.2.2, about donor testing, you indicate that the birth mother’s specimen is tested for treponemal specific assay for syphilis (b) (4) . Please note that if the birth mother tests reactive using a treponemal specific assay for syphilis, the donor should be determined ineligible regardless of any subsequent confirmatory test result (refer to 21 CFR part 1271.80(d)(1) and section VI.A of the 2007 Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM091345.pdf>.

In all donor testing-relevant SOPs and forms, you state that a donor is eligible if “reactive syphilis with negative confirmatory testing.” For example, Form 11.3.022-01-PU indicates that a donor with “reactive syphilis with negative confirmatory testing” is determined eligible and the CBU meets criteria for licensure. The statements “reactive syphilis with negative confirmatory testing” and “non-treponemal test for syphilis when specific treponemal confirmatory test is negative” in your documents, would only apply if you were utilizing a non-treponemal screening test for syphilis. Please revise all relevant sections of the BLA, SOPs and forms to specify that a donor with reactive test for syphilis (treponemal specific) is ineligible.

Applicant’s response: StemCyte provided the following response:

“The testing vendor previously offered a non-treponemal assay but revised their testing policy to include a treponemal-specific assay. When this change was implemented, not all affected documents were identified and updated. A careful review of all related or documents impacted by this changed and revisions have been made to reflect the use of only treponemal-specific assays. Donors who test positive are deferred from donation.”

Form 11.3.022-01-PU Donor Records Review Summary was revised to remove references to specific tests for syphilis.

Reviewer comment: The revised document is acceptable.

Complete Response Letter Comments 1e:

Regarding the final DE determination: It is unclear whether the DE determination is made by the Medical Director or designee before the HPC, Cord Blood is listed in the National Marrow Donor Program (NMDP) searchable inventory. In SOP 16.1.003-UN, the purpose of the SOP is “provide an overview of the review process to determine if a public cord blood unit is eligible for transplant.”

SOP 16.1.003-UN, Section 2 states the following:

- Applicant performs this donor eligibility determination during what we call the “2nd Review” of the donor/cord blood file folder. (See 16.1.006-UN (#G06)) At the end of this review, the donor eligibility determination and 2nd review are documented. If the donor is eligible and the 2nd review is satisfactory, the donor is made available for search in the NMDP Registry.”
- “2nd review of donor’s file folder. The 2nd review by the Medical Director or designee is the final step in donor eligibility. (See 16.1.006-UN (#G06), Product Review –Public Bank) This review covers all the information currently in the file folder, including donor history questions, maternal testing, and cord blood testing results. The results of this review and documentation of this review indicate that

the cord blood unit is no longer in quarantine and is now in permanent long-term storage.”

According to the above information, it appears HPC, Cord Blood is listed in the NMDP registry after the documentation of the DE determination by the Medical Director or designee in the “2nd Review”. However, we note the following discrepancies:

- Review flowchart submitted in Amendment 5 does not indicate that the “Final Donor Eligibility and Review” is performed by the Medical Director or designee. The flowchart indicates that the “MD Review” is completed before the HPC, Cord Blood is released for transplantation.
- The revised SOP 11.1.022-PU, section 2- Donor Eligibility Determination (Amendment 31) states “All cord blood units remain in quarantine status until the donor eligibility determination has been completed and determined to be eligible or ineligible by the responsible donor eligibility specialist.” It appears the HPC, Cord Blood may be released from quarantine by the “donor eligibility specialist” before review and documentation of DE determination by the Medical Director or designee.

Please address the following and submit the revised documents:

- i. Please confirm that the final DE determination is made and documented by the Medical Director or designee before the HPC, Cord Blood is released to the NMDP’s searchable inventory and clearly describe the steps in the SOPs.
- ii. If the DE determination is performed by a responsible person other than the Medical Director, please describe their qualification and medical training.
- iii. According to SOP 16.1.003-UN cord blood units from “ineligible” donors (e.g., positive for anti-HBc) can be designated as “transplantable” and made available for transplantation if there is an urgent medical need. Please note, that in case of an urgent medical need, such units may be made available for transplant under an investigational new drug application. Please revise and submit the SOPs and forms that clearly describe that such units do meet the acceptance criteria for licensure.

Applicant’s Response: StemCyte states that the Medical Director performs the donor eligibility determination by completing the Declaration of Donor Eligibility Form 11.3.022-

02-PU. StemCyte states “No Donor Eligibility determinations are made by any individual other than the Medical Director.” (Response to CR Letter dated 20 January 2023).

In addition, StemCyte states “SOP 16.1.003-UN was updated as a new document specific to public CBUs only (SOP 16.1.003-PU), clearly stating that ineligible units are not able to be licensed but may be made available for transplant under an IND and documentation of urgent medical need from the transplant physician.”

Reviewer comment: StemCyte revised their process for review of batch records and product release with the following:

1 - StemCyte provided a revised flowchart “Donor Records Review and DE Determination Process Flowchart”. The flowchart delineates clerical review, donor record review, DE determination and batch release.

2 - Descriptions of manufacturing process and process controls of the drug substance (3.2.S.2.2) and the drug product (3.2.P.3.3) were “revised/rearranged to better reflect the point(s) at which donor suitability and screening procedures are employed at collection sites during procurement. Language regarding determination of donor eligibility was removed from 3.2.S.2.2 [drug substance] and inserted into 3.2.P.3.3 [drug product].”

3 - StemCyte revised their description of the donor records review process and donor eligibility determination process. StemCyte created new forms and revised SOPs to delineate review processes, DE determination, and release for distribution. The donor record review is documented separately from the declaration of donor eligibility.

The summary of records form (16.3.007-04-PU) was created as part of the revised record review process. The communicable disease tests listed in a table on the form was incorrect. The revised form (revision 2) was submitted in Amendment 37.

The new procedures and revised forms are acceptable.

Complete Response Letter Comment 1f:

According to information submitted in amendments, we understand the following SOPs are being revised. Please submit the final SOPs.

- i. SOP 01.1.020-UN Chain of Custody for StemCyte Cord Blood Bank
- ii. SOP 04.1.082-PU Public Shipper Use and QC/PM
- iii. FORM 04.3.082-PU Shipper Daily QC/PM
- iv. SOP 10.1.008-PU NMDP Product Requests
- v. SOP 11.1.008-PU Donor Demographic Information and Health History Forms
- vi. SOP 12.1.006-PU Ex Utero Cord Blood Collections-Public
- vii. SOP 13.1.005-UN Maternal and CB Specimen Processing
- viii. SOP 14.1.010-PU Packing and Shipping Samples to (b) (4)

- ix. SOP 16.1.003-UN Availability of Public Cord Blood Units for Transplantation and Distribution-Shipping

Applicant's Response: StemCyte submitted revised documents.

Reviewer comment:

01.1.020-UN Chain of Custody for StemCyte Public Cord Blood Bank – Revision 2 was submitted in Amendment 35 in response to the CR Letter. Revision 3 was revised to include donor eligibility determination and product review processes as part of an information request and submitted in Amendment 36.

Other documents submitted as requested are acceptable.

Reviewer Comment to the Lead CMC Reviewer:

DHT has completed our review of information regarding donor eligibility in 21 CFR part 1271 subpart C. The applicant has effectively addressed all issues related to making a donor eligibility determination. DHT has no further comments for the sponsor at this time.