



Our STN: BL 125764/0

**COMPLETE RESPONSE**

January 20, 2023

StemCyte, Inc.

Attention: (b) (6)

(b) (6)

Dear Dr. (b) (6)

Please refer to your Biologics License Application (BLA) received January 7, 2022, for Hematopoietic Progenitor Cells, Cord Blood (HPC, Cord Blood) manufactured at your Baldwin Park, California location and submitted under section 351(a) of the Public Health Service Act.

We have completed our review of all the submissions you have made relating to this BLA, with the exception of the information in the amendment submitted and received December 21, 2022, as noted below. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

#### Chemistry, Manufacturing, and Controls

1. With reference to donor screening, donor testing and donor eligibility (DE) determination, we sent you multiple information requests (IRs) on the following dates: March 22, 2022, May 11, 2022, June 2, 2022, August 1, 2022, October 6, 2022, and November 10, 2022. However, your response to those IRs did not completely address the concerns we raised, and we need additional information from you to complete the review of this section. Therefore, please address the following:
  - a. 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.
  - b. 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 risk factors 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.

- c. 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.
- d. 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.

e. 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 CBUs 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 (IND). Please revise and submit the SOPs and forms that clearly describe that such units do not meet acceptance criteria for licensure.
  - f. According to information submitted in amendments, we understand the following documents are being revised. Please submit the following final SOPs and forms:
    - 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
2. In your August 24, 2022 response to our August 1, 2022 IR, you provided information limited to (b) (4) CBU collection sites and intend to qualify new CBU collection sites according to SOP 01.1.003-UN Critical Supplier Qualification. However, this SOP contains information only on material supplier qualification and not CBU collection sites. While Quality Manual 01.1.001-UN, v.9 contains some information on qualification of collection procedures, it does not entail the qualification of CBU collection sites. Given that you have not outlined the procedures used for the qualification of collection sites, we are unable to determine how you qualify collection sites. Therefore, please provide a detailed narrative and protocol on the procedures used for qualification of CBU collection sites, including new collection site(s).

3. You have not provided the protocol and report for the entire process validation (PV) beginning with CBU collection through thawing and washing of the product using the validated SOPs. During the original BLA review period, as a result of your responses to our numerous IRs, you significantly modified the methods used in the manufacture and quality control testing for cell viability, CD34 count, and sterility of HPC, Cord Blood. In addition, to address the below Complete Response comments, additional modifications to PV may be necessary. PV should provide objective evidence that the process consistently produces the product meeting its predetermined specifications. Given that you revised your methods for several product attributes and have not provided a PV protocol report covering the entire manufacturing process, we cannot determine if you can consistently manufacture HPC, Cord Blood with your updated manufacturing process. Please perform and provide a complete PV report with protocol incorporating your updated SOPs for your entire manufacturing process that address the following:
  - a. It appears that the CBUs used in your PV study were not consecutively collected and you may have provided data only on CBUs meeting specifications rather than consecutively collected CBUs. Please submit a revised/updated process validation protocol and report. The validation protocol should provide a detailed narrative of what will be executed and the pre-specified criteria (both in-process and final specifications) to be met. The process validation should cover collection, manufacture/processing, as well as the thawing and cryoprotectant removal post thaw from consecutively collected CBUs to demonstrate that you are able to consistently manufacture and thaw those HPC, Cord Blood that meet the in process and final product specifications. The validation report should contain a summary of the validation results after executing the validation protocol. Please provide a revised validation report.
  - b. In your PV study report, please include tables that contain acceptance criteria and results for pre-processing CBUs, post-processing HPC, Cord Blood and post-thaw and wash HPC, Cord Blood drug product.
  - c. Please list deviations, if any, noted (including the CBUs that failed the in-process and final release criteria) during the entire PV and summarize your plans to prevent such deviations in the future.
4. In your October 31, 2022 response to our IR dated October 18, 2022, you submitted a revised (b) (4) viability SOP 14.1.040-PU and assay validation report without providing any supporting narratives on what was revised or an explanation for the changes. In addition, the procedures in the revised SOP 14.1.040-PU and the validation report do not match. Your (b) (4) viability assay does not provide assurance that you would be able to reproducibly perform the assay. Please provide a revised (b) (4) validation protocol and

report. The validation protocol should contain a detailed description of what will be executed for all the parameters assessed and the pre-specified criteria that would be met. The validation report should contain a summary of the results obtained after execution of the validation protocol, any deviations encountered and their resolutions as well as conclusions of the validation study. In addition, the study should address the following:

- a. Please provide a summary of the changes you implemented and the rationale for these changes to the revised (b) (4) viability assay.
  - b. In the revised (b) (4) viability assay validation report, you did not establish a limit of quantitation of 0% viability. Please establish a limit of quantitation for the (b) (4) viability assay. A 0% viability can be attained by methods such as heat treatment of cells in a  $\geq 60^{\circ}\text{C}$  water bath.
  - c. Please submit the (b) (4) viability assay validation report with data obtained with thawed cord blood samples. The validation report should include the validation protocol, as well as a detailed description of how the assay was executed and the pre-specified criteria. The validation report should also contain a summary of the results in tabular form and a discussion of any deviations encountered.
  - d. You established the post-thaw viability for total nucleated cells (TNC) at (b) (4). The post-thaw TNC viability of (b) (4) does not meet the criterion of  $\geq 70\%$  for post-thaw TNC viability described in FDA's 2014 guidance titled, "Biologics License Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System" (Cord Blood Licensure Guidance) available at <https://www.fda.gov/media/86387/download>. Please update your post-thaw TNC viability criterion to reflect the acceptable level of 70% or greater, as described in the guidance.
  - e. Since your process validation and stability studies were conducted with the previous unrevised SOP, please conduct these studies with the revised viability assay SOP and submit this data.
5. With reference to the (b) (4) assay validation, please address the following:
- a. The section titles and the descriptions in SOP Validation ID: CSR-0044-02 and validation report CSSR-0044-02 are not consistent with the respect to the scope of the SOP.
    - In your SOP Validation ID: CSR-0044-02, Section 1.0, you state that "this characterization study" is applicable to (b) (4) assay

performed at StemCyte Inc.,” and in Section 3.0, you describe the scope of the validation as “the equipment/systems and all associated components listed in section 1.”

- In the Validation Summary Report: CSSR-0044-02, Section 1.2, you state that “This Characterization Study is applicable to (b) (4) assay performed on post-processing sampling of red cell reduced RCR Cord Blood units CBUs.”

Please revise your (b) (4) assay validation sections, so that the narrative details provided in the described sections match/reflect the respective titles.

- b. In your October 31, 2022 response to our IR dated October 18, 2022, you indicated when a (b) (4) test well shows contamination on repeat testing and the sterility results on the CBU is negative, the (b) (4) assay is repeated using a post-(b) (4) sample. It is not clear which post-(b) (4) sample you are using for your repeat testing. Please describe the source of the (b) (4) sample used for the repeat (b) (4) assay when one of the duplicate assay (b) (4) on the post-processing sample is contaminated.
  - c. Please revise the following sections of the (b) (4) SOP 14.1.015-UN (Cord Blood Hematopoietic (b) (4) Assay):
    - i. In Section 3.0, please clarify the statement that “cord blood samples should not exceed 48 hours after collection.”
    - ii. In Section 4.0, you submitted a product insert for (b) (4) yet you state (b) (4) from (b) (4) is used. Please submit the correct product insert for the (b) (4)
    - iii. In Section 6.0, please clarify what is being thawed for (b) (4) in ‘Step (b) (4)
    - iv. Please update the SOP with your response to procedures followed when an assay well is contaminated, as noted in part 5b above.
6. Please address the following concerns with the Thaw and Wash for RCR Process Validation report (PV-0013-01-ADD01):
- a. Your validation report states that you are following (b) (4) (b) (4) sterility test methods, but you did not provide information on the test sample volume. Please provide information on the test sample volume used for this sterility testing. If you are not using test sample volume per (b) (4) please validate your method and provide a report.

- b. The HPC, Cord Blood test sample used for sterility testing for your thaw and wash validation may contain residual amounts of dimethyl sulfoxide (DMSO). DMSO may confound the results of sterility testing and mask a potential positive sterility result during your PV. If sterility test samples contain DMSO, you should provide data from bacteriostasis and fungistasis studies to demonstrate that the use of DMSO does not interfere with the detection of bacterial and fungal contaminants. The sterility test method used in the bacteriostasis and fungistasis studies should be the same method used to test your product. Please refer to (b) (4) sterility test methods for a description of appropriate test methodology.
7. In Section 3.2.S.2.2.3, “Fresh CBU storage and transportation,” you state, “the shipping containers have been validated to maintain an internal temperature between (b) (4) in both (b) (4) temperature profile extremes for both minimum and maximum loads, if packed in accordance to written procedures.” However, you did not provide the validation report conducted in both (b) (4) temperature profile extremes for the CBUs. We need this report to ensure that the (b) (4) shipper maintains the internal temperature for the specified period under temperature extremes. Please provide the CBU storage and transportation validation report performed at (b) (4) (b) (4) temperature extremes with the (b) (4) shippers.
8. In SOP 13.1.026-PU, “Cord Blood Unit Sample Receipt and Accessioning,” you state, “if the CBUs does not meet the pre-processing acceptance criteria, the lab manager or the CBB Medical Director will make the final decision on whether the cord blood unit should remain stored or discarded.” You did not provide any details about the criteria the lab supervisors will use to determine if CBUs not meeting the pre-processing specification should be processed. In addition, you did not clearly indicate the pre-processing acceptance criteria for fresh CBUs. Therefore, we cannot determine whether your pre-processing acceptance criteria are adequate. Please address the following:
  - a. Please explain the criteria that will be used by the supervisor or lab manager or Cord Blood Bank (CBB) medical director to use or discard the pre-processed CBU with appropriate justification.
  - b. Please provide a table of parameters with acceptance criteria for pre-processed CBUs.
9. In SOP 14.1.039-PU, you indicate that the Medical Director reviews (b) (4) test results with (b) (4) (b) (4) (b) (4) (b) (4). While it appears that the Medical Director decides on whether these units are used, the basis used to make decisions on these units and the procedures you follow regarding the dispositions of these units are not clear.



Therefore, please describe how CBUs with (b) (4) (b) (4) are handled and discuss the decision-making process to dispose of these units. Also based on this statement, it appears you have an in-process criteria for (b) (4) as a control for your manufacturing, but you did not describe in-process criteria. Please describe these criteria.

10. For the stability program for HPC, Cord Blood product, you have not provided appropriate documents that describe which protocol would be followed to establish a longer product expiration. Furthermore, it is not clear which protocol was executed to generate the submitted stability data. Please address the following:
  - a. Please submit a stability protocol that describes how you executed the stability study in support of the expiration date.
  - b. Please submit a stability study report in support of the expiration date. The report should include a summary of the results obtained and any deviations and explanation/discussions of the results.
  - c. Please submit a stability protocol that will be executed yearly to establish longer product expiration. The protocol should specify the number of units that will be thawed, the pre-specified criteria to meet, and how the study will be conducted. Please be advised that you will need an approved stability protocol in the BLA that will be executed annually to advance the expiry of the HPC, Cord Blood product.
  - d. In the stability protocol and report, please refer to the appropriate SOP (number and title) that describes the assays you perform rather than duplicating the same SOP.
  - e. In your table titled, “2022 CBU Stability Summary for RCR units,” in support of expiration dating of your HPC, Cord Blood product, you provided two entries for “Post-thaw (b) (4)” and “Post thaw (b) (4)” The results entered for the first set of ‘Post thaw (b) (4)’ and ‘Post thaw (b) (4)’ are entered as N/A without any explanation. Please clarify these entries for (b) (4) and the ‘post-thaw’ results in support of your HPC, Cord Blood product stability.
11. In SOP 16.1.002-UN, you indicate that you retain a maximum of (b) (4) (b) (4) of umbilical cord tissue as retention samples. However, umbilical cord tissue alone is not a representative of each HPC, Cord Blood. As outlined in 21 CFR 211.170(b)(1), an appropriately identified reserve sample that is representative of each lot or batch of drug product shall be retained and stored under conditions consistent with product labeling. In addition to the umbilical cord tissue, you should retain other samples that are appropriately identified and representative of HPC, Cord Blood. Therefore, please provide a plan for retaining product

samples that are appropriately representative of HPC, Cord Blood. Please note that these samples must be retained and stored at temperatures and under conditions that will maintain their identity and integrity and are consistent with product labeling for one year after the expiration of the HPC, Cord Blood.

12. In SOP 17.1.005-UN, “Thaw and Wash for Red Cell reduced (RCR) Units,” you indicate that the final product is stored in a refrigerator at 2° C to 8° C until transplantation and the infusion time should not exceed 2 hours post-thaw. However, you did not submit data to support the holding temperature of 2°C to 8°C for a maximum of 2 hours. To support the proposed holding conditions, you should provide validated data for holding temperature and time. An expiration time should be based on this validation study that accounts for the maximum time for infusion. Your thaw and wash validation report should support the conditions you describe (i.e., holding the HPC, Cord Blood at 2°C to 8°C until transplantation). Please submit the thaw and wash validation report to support the holding temperature and time.
13. In your SOP 14.1.027-UN for “HLA Sample Preparation and Shipping to (b) (4) you include ‘oral swabs’ as samples for HLA-typing and include (b) (4) (b) (4) as a supply used in the assay. As described in our cord blood licensure guidance (<https://www.fda.gov/media/86387/download>), ‘oral swabs’ is not an appropriate sample for HLA-typing. HLA-typing should be performed on cord blood from attached segments of HPC, Cord Blood. In addition, there is no step/section in the SOP describing how the (b) (4) is used. Please revise your SOP to be consistent with our cord blood licensure guidance and clarify the purpose of the (b) (4).
14. You mention that for confirmatory HLA-typing at (b) (4) stored samples will be used and that sample preparation for shipping to (b) (4) follow SOP 14.1.012-UN (Shipping of Samples for confirmatory HLA Typing). Please address the following:
  - a. Please be aware that Confirmatory HLA typing should be done on contiguously attached segment and not on stored samples. Please revise your sampling strategy and SOP accordingly.
  - b. You did not submit this SOP. Please submit SOP 14.1.012-UN Shipping of Samples for confirmatory HLA-Typing.
15. In Section 3.2.P.3.3, Table 1, you did not include CD34<sup>+</sup> cell count in the HPC, Cord Blood Unit Release Specifications. As described in our cord blood licensure guidance, CD34<sup>+</sup> cell count is a critical parameter for the quality of HPC, Cord Blood. Therefore, please include total CD34<sup>+</sup> cell count as part of HPC, Cord Blood unit release specification and revise Table 1 in Section 3.2.P.3.3 accordingly.

16. For the CD34+ flow cytometry assay used as a part of product release, (b) (4) package insert for CD34 Enumeration Kit recommends (b) (4) (b) (4). However, in SOP 14.1.023-UN, revision 2, Section 6.13, you are proposing to (b) (4) (b) (4). It is not clear whether deviating from the suggested package insert (b) (4) will affect the accuracy of your enumeration. Please provide a justification for choosing (b) (4) threshold for (b) (4) the CBU and not using (b) (4) recommended threshold for (b) (4).
17. With reference to CSR 0083-02 submitted on October 21, 2022 (SN0025), in response to our IR dated July 27, 2022, you performed (b) (4) (b) (4) with expected outcomes of (b) (4) respectively. However, it is unclear why you performed (b) (4) of only up to (b) (4). If the purpose of this study is to find the limit of detection, then you should (b) (4) (b) (4) until you are able to achieve the limit of detection. Please provide a justification for your (b) (4) and provide data to determine the lower limit of detection.
18. In section 3.2.S.4.1, Table 1, you indicate that donors meet criteria defined in “CFR 1270.21.” However, for human cells, tissues, or cellular or tissue-based products (HCT/Ps) recovered (collected) after May 25, 2005, a donor eligibility determination must be made, as specified in 21 CFR 1271 Subpart C. Therefore, please revise this table accordingly and submit the revised table.
19. You requested categorical exclusion for environmental assessment under 21 CFR 25.31(j). However, your product is not classified under transfusable human blood or blood components and plasma. Therefore, please provide a request for categorical exclusion under 21 CFR 25.31(c) for marketing approval by revising this section in your submission.

Outstanding inspectional issues relating to the pre-license inspection (PLI) performed at your Baldwin Park, CA facility from August 29 to September 2, 2022:

20. Your media simulation studies were insufficient, as they do not confirm the absence of microbial contamination throughout the entire process. Per Amendment 31 received November 22, 2022, you confirmed that all of the media from each of the media simulation runs was sent to the contract tester. However, you noted that the contractor took aliquots from each of the different (b) (4) of media (each (b) (4) representing a different stage of processing) for sterility testing. There is no confirmation that the entire volume of media was (b) (4) incubated for growth. The sterility test results (passing) confirm the absence of microbial contamination in the aliquots only, and do not demonstrate the absence of microbial contamination throughout the process. Media simulation studies require that all of the media be incubated to ensure the absence of microbial contamination throughout the process. Please confirm that the entire volume of media for all of the microbial simulation runs was (b) (4) incubated for growth,

or submit a summary of the protocol and report, including data, for a new media simulation study. Please also indicate the frequency and conditions in which your procedure would require a new media simulation study.

21. Your master batch record provided in the BLA and as observed during the pre-license inspection is not sufficiently detailed. Please provide a copy of the revised master batch record that reflects the most updated information regarding manufacturing procedures, steps, and acceptance criteria. The master batch record should also provide for linkage of the StemCyte lot number to the NMDP number, local cord blood unique identification (CBUID) number, and the International Society of Blood Transfusion (ISBT) number, as applicable.
22. The environmental monitoring (EM) action limit for microbial surface and passive air (b) (4) for your biological safety cabinets (BSC) does not meet the recommended acceptance criterion of (b) (4) (b) (4) for ISO (b) (4) BSCs. Please provide a justification for your action limit.
23. Your procedures do not refer to the correct regulations and Current Good Manufacturing Practices (CGMP) operating system for HPC, Cord Blood. Draft SOP 07.1.001-06-UN, Reporting of Biological Product Deviations, with four SOP attachments was submitted to the BLA in Amendment 29, received November 14, 2022, in response to the PLI Form FDA 483 Observation #11c. This SOP and its attachments collectively refer to 21 CFR Part 606 including 21 CFR 606.171, and 21 CFR Part 820. Draft SOP 07.1.001-05-UN, Complaint Management, and draft Form 07.3.001-06-UN, Customer Complaint Form, were submitted to the BLA in Amendment 29, in response to the PLI Form FDA 483 Observation #11d. This SOP refers to 21 CFR Part 820.198. Please note that 21 CFR 606.171 is a provision within the blood and blood components CGMPs, and is not applicable to HPC, cord blood. Likewise, 21 CFR Part 820 is the Quality System Regulation and establishes the CGMPs for devices. Part 820 is not applicable to HPC, Cord Blood. Please be advised that your HPC, Cord Blood product is regulated as a biological drug product and as such, must meet the applicable general biological standards within Part 600 as well as the applicable CGMP requirements within Part 211. Please ensure all SOPs and their attachments submitted in response to Observation #11 meet the applicable requirements and CGMPs for your HPC, Cord Blood product; specifically, please submit:
  - a. A revised SOP 07.1.001-06-UN, Reporting of Biological Product Deviations, including any attachments, that addresses the applicable requirements established per 21 CFR 600.14, Reporting of biological product deviations by licensed manufacturers; and
  - b. A revised SOP 07.1.001-05-UN, Complaint Management, and Form 07.3.001-06-UN, Customer Complaint Form that addresses the applicable

requirements established per 21 CFR 211.198, Reporting of biological product deviations by licensed manufacturers.

#### Labeling

24. We reserve comment on the proposed labeling until the application is otherwise acceptable. We may have comments when we see the proposed final labeling.

Within one year after the date of this letter, you are required to resubmit or withdraw the application (21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval.

Please submit your meeting request as described in CBER's SOPP 8101.1 *Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants* at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm>, or may be requested from the Office of Communication, Outreach, and Development, at (240) 402-8020.

We acknowledge receipt of your amendment dated December 21, 2022 . Please be aware that we have stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response. You may cross reference applicable sections of the amendment dated December 21, 2022, in your complete response to this letter and we will review those sections as a part of your complete response.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Jennifer Albert, at (301) 837-7230 or by email at [Jennifer.Albert@fda.hhs.gov](mailto:Jennifer.Albert@fda.hhs.gov).

Sincerely,

Heather Lombardi, PhD  
Director  
Division of Cellular and Gene Therapies  
Office of Tissues and Advanced Therapies  
Center for Biologics Evaluation and Research