



U.S. Food and Drug Administration  
 Center of Biologics Evaluation and Research  
 Office of Compliance and Biological Quality  
 Division of Manufacturing and Product Quality  
 10903 New Hampshire Avenue, Silver Spring MD 20993  
[www.fda.gov](http://www.fda.gov)

**To:** Administrative File: BLA STN 125764/0.35 for RegeneCyte – CR Addendum Review

**From:** Xiuju Lu, Chemist, CBER/OCBQ/DMPQ/MBR3

**Through:** CDR Donald Ertel, Branch Chief, OCBQ/DMPQ/MBR3

**CC:** Carolyn Renshaw, Division Director, CBER/OCBQ/DMPQ  
 Gregory Price, Team Lead, OCBQ/DMPQ/MBR3  
 Iryna Zubkova, RPM, OCBQ/DMPQ/MBR3  
 Jennifer Albert, RPM, CBER/OTP/ORMRR/DRMRR1/RRB1

**Sponsor:** StemCyte, Inc. (US License No. #2280)

**Facility:** 13800 Live Oak Ave. Baldwin Park, CA. 91706 USA (FEI # 3003562296)

**Product:** RegeneCyte [Hematopoietic Progenitor Cell, Cord Blood (HPC, Cord Blood)],  
 Injectable Suspension

**Indication:** Unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system

**Subject:** Addendum DMPQ review memorandum for Biologics License Application filed per 21 CFR 601.2 [Evaluation of StemCyte’s response to the Complete Response (CR) letter issued on January 20, 2023]

**ADD:** May 9, 2024

**Signature Block:**

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Xiuju Lu, DMPQ Reviewer CBER/OCBQ/DMPQ/MBR3	Concur	
CDR Donald Ertel, Branch Chief CBER/OCBQ/DMPQ/MBR3	Concur	
Carolyn Renshaw, Division Director CBER/OCBQ/DMPQ	Concur	

## RECOMMENDATION:

Based on the reviewed information provided in the submission, approval of this BLA is recommended.

StemCyte's response to the Complete Response Letter issued January 20, 2023 for deficiencies #20-23 under DMPQ purview appears acceptable. The pre-license inspection (PLI) results combined with the firm's Complete Response (CR) amendment and the information request response support the approval of BLA STN 125764/0.

## SUMMARY (Timeline)

- January 7, 2022: CBER received submission of BLA STN 125764/0 for Hematopoietic Progenitor Cell, Cord Blood (HPC, Cord Blood), minimum of  $9.0 \times 10^8$  total nucleated cells injectable suspension (RegeneCyte).
- August 29 – September 22, 2022: CBER conducted a pre-announced PLI at StemCyte facility, located at 13800 Live Oak Ave. Baldwin Park, CA. 91706 USA (FEI # 3003562296), in support of review of BLA 125764/0. At the conclusion of the PLI, an eleven-item FDA 483 observation memo was completed.
- January 20, 2023: Primary DMPQ review was completed by Xiuju Lu. A complete response (CR) was recommended due to unresolved 483 observations noted during the PLI. CBER issued a CR letter to the BLA which identified a total of twenty-four deficiencies. Items #20-23 in the CR letter specified the deficiencies under DMPQ purview.
- November 9, 2023: StemCyte submitted amendment STN 125764/0.35 as a response to the FDA's CR letter issued on January 20, 2023.
- January 26, 2024: Combined Information Request (IR) was issued to StemCyte (Question 12 was from DMPQ regarding clarification on media fill studies).
- February 9, 2024: StemCyte responded to the above IR in STN 125764/0.37.

StemCyte provided responses to all twenty-four deficiencies in the CR letter response. The firm additionally updated Module 3 reflecting the CAPAs and content updates / revisions to the PLI observations.

Deficiencies #20-23 are under DMPQ purview. The rest of deficiencies are under the purview of Product Office, Office of Therapeutic Products (OTP), clinical, preclinical or labeling disciplines.

## REVIEW

### I. Responses to CR Letter Deficiencies

#### CR Letter Deficiency #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 cultured/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.

**Firm's response:**

The HPC Cord Blood product is manufactured in StemCyte using (b) (4) Red Cell Reduction (RCR) method and addition of cryoprotectant using (b) (4) (b) (4) cryopreservation using (b) (4)

The following three documents were provided in the response to CR Letter Deficiency #20:

- SOP 14.1.019-PU *Media-Fill Aseptic Processing* (v3, effective on May 1, 2023).
- Executed batch record PV-0070-03 (effective June 12, 2023).
- Media Fill validation report PVSR-0070-03 (effective August 13, 2023).

The media fill was performed in July 2023 using (b) (4) with (b) (4) runs in total (b) (4) runs for (b) (4) equipment, (b) (4) All media from final products (cryobags) and in-process containers (b) (4) were collected during the media fill and sent to the 3<sup>rd</sup> party contractor (b) (4) for sterility and growth promotion testing. Growth promotion was tested using the same lot post-sterility test media and (b) (4) in (b) (4) The microorganisms challenged in growth promotion tests include (b) (4) The acceptance criteria for the media fill runs were: (b) (4)

Routine environmental monitoring performed in media fill runs included viable surface and particulate air sampling in biosafety cabinets (BSCs) as well as viable surface sampling for public workbench. The acceptance criteria of viable surface testing in BSC were 'devoid of contamination.'

The simulated media collected in (b) (4) (b) (4) cryobags were all negative after (b) (4) in (b) (4) Growth promotion showed positive results within (b) (4) days of (b) (4) for all tested microorganisms in (b) (4) media fill runs. The environmental monitoring results of settling plates in BSC (acceptance criteria (b) (4)) and the (b) (4) microbial surface monitoring in the public area (b) (4) spots tested in total) within the (b) (4) of media fill runs met the predefined acceptance criteria (b) (4)

Media fill will be performed every (b) (4) in StemCyte after initial qualification. A new media simulation study will be performed upon changes of new (b) (4) processing procedure, processing locations, or excursions of product contamination that impact the aseptic process. The media simulation is also used as part of competency evaluation for lab technicians.

**Reviewer's Comments:** StemCyte collected the whole volume of media for (b) (4) testing and performed growth promotion testing in the media fill study. The (b) (4) was used in place of (b) (4).  
(b) (4) The reported results on (b) (4) growth promotion and environmental monitoring appeared acceptable.

*The following remains unclear in the original amendment STN 126764/0.35 regarding media fill: (1) the in-process operation time limits for each step in HPC Cord Blood manufacture; whether the maximum durations were challenged in the media fill runs; (2) there was no description of interventions (inherent & corrective) performed in the media fill; (3) the firm didn't specify whether they will identify to species in case that positive results occurred in a media fill run.*

The firm responded to a combined IR in STN 125764/0.37 with the following regarding media fill (note – the IR was issued on January 26, 2024): (1) the duration limits for critical operations in HPC, Cord blood production, including steps of (b) (4) operation/disconnection and cryoprotectant infusion; (2) the maximum operation duration was set up to (b) (4) depending on the volume of cord blood collected for HPC, Cord blood manufacture. The completed media fill studies were shorter than the maximum operation time by (b) (4). StemCyte revised the media fill protocol to use (b) (4) media in future media fill studies to cover the maximum operation time; (3) routine interventions were performed in the media fill studies. In cases where operations deviate from standard operation procedures or leaking occurs, the HPC, Cord blood will be discarded, therefore, no corrective interventions were performed in the media fill simulation study; (4) any positive growth in media fill studies will be identified to species level.

**Reviewer's Comments:** StemCyte's responses to the IR questions regarding media fill studies appear to be acceptable.

#### **CR Letter Deficiency #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.

#### **Firm's response:**

A new SOP, 06.1.014-PU *Production Batch Record Preparation and Release for Manufacturing* (v2, effective October 30, 2023) was created in StemCyte for batch record management. The SOP defines the procedures of preparation, generation, assembly, issuance, review and release of Production Batch Record (PBR) for HPC Cord Blood production in StemCyte. The Document Control or Quality Control specialists are responsible for preparation and generation of the PBR and ensuring the correct versions and effective dates before issuance of the PBR to the manufacturing operators.

The PBR includes multiple forms organized in the order of operation steps for public HPC Cord Blood production. A copy of the PBR is provided in the addendum. Revisions are made in Form 13.3.001-02-PU *The (b) (4) RCR Individual Processing Log -Public Bank* to include the local cord blood unique identification, the International Society of Blood Transfusion (ISBT) number, the NMDP number, and the maternal barcode number on the first page of form for tracking and minimizing mix-ups. In addition, the firm added details in Form 13.3.002-01-PU, *The Cord Blood Processing Worksheet*, for recording of (b) (4)

StemCyte provided the following documents in their response to CR Question #21:

- SOP, 06.1.014-PU *Production Batch Record Preparation and Release for Manufacturing* (v2, effective October 30, 2023).
- Form 16.3.002-01-PU *Public Storage Location Log* (v1, May 1, 2023).
- Master Batch Record for public HPC cord blood production in StemCyte.

**Reviewer's Comments:** *The information on the batch record management and the revisions with the PBR appears acceptable from DMPQ's perspective.*

(b) (5), (b) (7)(E)

#### **CR Letter Deficiency #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) for ISO (b) (4) BSCs. Please provide a justification for your action limit.**

#### **Firm's response:**

The action limit for microbial surface and passive air monitoring for BSC was changed to the recommended acceptance criterion of (b) (4) in Section 7 of SOP 08.1.002-UN.

SOP 08.1.002-UN *Microbial Surface and Passive Air Monitoring of Biological Safety Cabinets* (v4, effective on December 15, 2022) is provided in the addendum.

**Reviewer's Comments:** *The revised acceptance criteria of viable surface and passive air in BSCs (ISO<sup>(b) (4)</sup> is acceptable.*

**CR Letter Deficiency #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.

**Firm's response:**

SOPs and Forms are revised and updated as follows:

- SOP 07.2.001-05-UN, *Complaint Management and Biological Product Deviations* (v1, effective October 30, 2023) is revised to refer to 21 CFR 211.198(a) for all written and oral complaint and BPDR handling regarding the HPC Cord Blood product. It is noted that SOP 07.1.001-06-UN is merged into SOP 07.1.001-05-UN in this addendum.
- The Firm additionally provided file 07.2.001-06-UN (v1, effective November 21, 2022) illustrating on how to register a complaint record and to generate a Unique ID Complaint Number using the CQ Complaints Module; Form 07.3.001-06-UN (draft) is used as a job aid to log the complaints into the CQ eQMS complaints module.
- FDA Forms 3486 (4/23) *Biological Product Deviation Report* (BPDR) and Form 3500A (10/15) *MedWatch* are used in reporting of field product deviations and complaints.

**Reviewer's Comments:** The firm's response to CR Question 23 regarding regulation reference to BPDR and complaint management in StemCyte appears to be acceptable.

## II. Updates to eCTD Module 3 (STN125764/0.35)

The following updates in eCTD Module 3 are pertinent to DMPQ purview:

- 3.2.S.2.1 *Drug Substance Manufactures is updated.* (b) (4) [REDACTED] are listed for collection of CBUs and maternal blood samples (deferred to the Office of Therapeutic Products, OTP, to review).
- 3.2.S.2.2 *Description of Manufacturing Process and Process Control for Drug Substance.* The SOPs and forms used for screening, testing, and determining eligibility of umbilical cord blood donors are updated (deferred to OTP to review).
- 3.2.S.4.1 *Drug Substance Specification* (deferred to OTP to review).
- 3.2.P.3.3 *Description of Manufacturing Process and Process Control for Drug Product.* The Firm added a section 3.2.P.3.3.2 *Donor Eligibility Determination* (deferred to OTP to review)
- 3.2.P.8 *Stability.* The sections are updated on stability summary and conclusion (3.2.P.8.1), post-approval stability protocol and stability commitment (3.2.P.8.2), and stability data (3.2.P.8.3). Stability study is now performed on a minimum of (b) (4) HPC Cord Blood products processed by the (b) (4) Red Cell Reducing method and within a similar age (12 months). A visual inspection is performed on the frozen cryobags (b) (4) (acceptance criteria (b) (4) [REDACTED]). The thawed frozen cord blood products are tested for sterility (acceptance criteria 'no growth'). The updated data included testing results on (b) (4) batches of HPC Cord Blood products that were frozen for 142-143 months (cryopreserved since (b) (4) [REDACTED]). The testing results on integrity of the cryobags and sterility both met predefined acceptance criteria.
- 3.2.A.1 *Facilities and Equipment.* The facility for hemoglobinopathy testing of the cord blood samples is changed from (b) (4) [REDACTED]

**Reviewer's Comments:** During stability studies, the firm controls the integrity of the frozen (b) (4) prior to thawing and the sterility of samples after thawing. The visual inspection of bag integrity and the sterility results on the (b) (4) stability samples thawed from the 2011 frozen products appears to support the proposed current shelf-life from a DMPQ perspective. The remaining information on product quality and related method validation in module 3.2.P.8 (STN 125764/0.35, November 9, 2023) is deferred to OTP to review.