



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

To: Administrative File: BLA STN 125743/0.68 for ALYGLO- Amendment Review

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

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

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Sponsor: Green Cross Biopharma Corp. (GCBP) (US License #: 2033)

Facility: 586 Gwahaksaneop 2-ro, Ochang-eup, Cheongwon-gu, Cheongju-si, Chungcheongbuk-do, Republic of Korea, 28119 (FEI # 3009561235)

Product: ALYGLO [Human Immune Globulin Intravenous (IGIV), 10% Liquid]

Indication: For the treatment of primary humoral immunodeficiency

Subject: Addendum DMPQ review memorandum for Biologics License Application filed per 21 CFR 601.2 [Evaluation of GCBP's response to the Complete Response (CR) letter issued on February 25, 2022]

ADD: January 13, 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.

GCBP's response to the Complete Response Letter issued February 25, 2022 for deficiency #1 under DMPQ purview appears acceptable. The pre-license inspection (PLI) results support the approval of BLA STN 125743/0.

SUMMARY (Timeline)

- February 25, 2021: CBER received submission of BLA STN 125743/0 for Human Immune Globulin Intravenous (IGIV), 10% liquid with filling sizes of 50 mL, 100 mL or 200 mL (ALYGLO).
- October 27 – November 16, 2021: CBER performed a Remote Interactive Evaluation (RIE) at GCBP, located at 586 Gwahaksaneop 2-ro, Ochang-eup, Cheongwon-gu, Cheongju-si, Chungcheongbuk-do, Republic of Korea 28119 (Ochang), in support of review of BLA 125743/0. At the conclusion of the RIE, an eleven-item RIE observation memo was completed.
- February 25, 2022: Primary DMPQ review was completed by Xiuju Lu. A complete response (CR) was recommended due to the conclusion from the RIE that an onsite Pre-License Inspection (PLI) was necessary prior to approval of the BLA. On the same day, CBER issued a CR letter to the BLA which identified a total of two deficiencies. Deficiency #1 in the CR letter specified the requirement of PLI at Ochang establishment to support approval of the subject BLA.
- January 14 – October 31, 2022: GCBP submitted quarterly updates (amendments 48, 59, 61 and 63) of corrective and preventive actions (CAPAs) and the global remediations to address the RIE observations issued on November 16, 2021 (see addendum memo dated November 29, 2023, Xiuju Lu)
- The Firm reported official name change from Green Cross Corporation (GCC) to Green Cross Biopharma Corp. (GCBP) in STN 125743/0.60, June 14, 2022.
- April 17 - 28, 2023: CBER conducted a pre-announced PLI at the Ochang Plant. An FDA Form 483 with three inspectional observations was issued to GCBP at the conclusion of the inspection.
- July 14, 2023: GCBP submitted amendment STN 125743/0.68 as a response to the FDA's CR letter issued on February 25, 2022, and the CR extension grant letter issued on February 21, 2023.

GCBP provided responses to both deficiencies in the CR letter response. The Firm additionally updated Module 3 in the same amendment reflecting the global remediations to the RIE observations, and the CAPAs following both the RIE and the PLI.

REVIEW

I. Response to CR Letter Deficiency #1

CR Letter Deficiency #1: Based on the manufacturing activities observed, the translated documents reviewed, and the interviews of GCC (*note*- name changed to GCBP since June 2022) personnel during the RIE, the Center for Biologics Evaluation and Research (CBER) has been unable to determine that the Ochang establishment complies with the standards established in the BLA and the requirements prescribed in the applicable regulations. Therefore, a pre-license inspection (PLI) of the Ochang establishment is deemed necessary to support the review and approval of the subject application.

We acknowledge the responses to the deficiencies submitted by GCC, including the enlistment of third-party consultants to assist with remediation efforts and your commitment to update CBER on the progress of these efforts.

Firm's response:

The PLI of Ochang plant was conducted from April 17 to April 28, 2023, to support the approval of ALYGLO. In response to the Form FDA 483, GCBP addressed the inspectional observations in the 15-day response (SN0071) which was submitted on May 19, 2023.

Reviewer's Comments: *GCBP has implemented corrective and preventive actions (CAPA) and addressed all the Form FDA 483 inspectional observations. (b) (7)(E), (b) (5) [REDACTED] at Ochang site ('DMPQ FDA 483 response review memo' by Xiuju Lu et al, July 18, 2023). The review of the CR letter deficiencies #2 is deferred to the product office (Office of Therapeutic Products, OTP). Details of the 2023 PLI including the inspectional observations at Ochang facility are described in the Establishment Inspection Report (EIR) 'EIR-GCBP-Apr 17-28-2023 XL GP MN RZ'.*

Based on the results of a holistic evaluation of the BLA, including the on-site PLI conducted in April 2023, the 15-day response to the FDA 483 observations and the Firm's CR letter response, GCBP appears to have established compliance with the standards established in the BLA and the requirements prescribed in the applicable regulations, and adequately addressed the inspectional observations in Form FDA 483.

II. Updates to eCTD Module 3 (STN125743/0.68)

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

- Aseptic Process Simulation (APS) re-validations performed in 2022 and in 2023 for 10% IGIV manufacture on filling line (b) (4) (3.2.P.3.5).
- Results of batch analysis for the Continued Process Validation (CPV) lots (3.2.P.5.4).
- Release and stability data were provided on following: (1) 36 months long-term stability data for the 2020 Process Performance Qualification (PPQ) lots of ALYGLO; (2) 12 months long-term stability data for a CPV lot (b) (4) manufactured in November 2021 for process robustness study; (3) 6 months long-term stability data for a CPV lot (b) (4) manufactured in August 2022 for the intermediate storage time confirmation study (*note*- the proposed long-term storage conditions for the 10% IGIV drug product are 24 months at (b) (4) -25°C and 36 months at 5±3°C). In addition to the stability data for drug product lots, GCBP also provided data for (b) (4) (b) (4) (b) (4) (b) (4)

time confirmation study; (4) release data for the (b) (4) lots of ALYGLO manufactured during the 2023 PLI (PLI lots, (b) (4) (3.2.P.8).

- The facility and equipment updates on the following: (1) changing of (b) (4) agents (b) (4) (b) (4) (due to product discontinuation; vendor remains unchanged); (2) switching the (b) (4) frequency (using (b) (4) from (b) (4) (b) (4); (3) updated the procedure to use (b) (4) removing disinfectant residues during cleaning; (4) updated the procedures of cleaning effectiveness verification and product changeover etc.; the cleaning verification report for the implemented changes in building (b) (4) was provided (GC-REP-00133) (3.2.A.1). (5) updated the flows of personnel, product, raw materials and wastes for ALYGLO manufacture in Ochang.

Reviewer's Comments: *The above-described facility and equipment updates in eCTD module 3, including APS, cleaning validation / verification, flows of personnel, product, raw material and wastes etc., have been reviewed and communicated to the firm during the PLI (reference to 'EIR-GCBP-Apr 17-28-2023 XL GP MN RZ' by Xiuju Lu et al). Observations in the PLI have been addressed in the firm's FDA 483 response, which was reviewed as adequate in the afore-mentioned 483 response review memo.*

Regarding stability study, firm provided bioburden and endotoxin testing results for the described (b) (4) drug product lots. All testing results met pre-defined acceptance criteria per specifications without excursions. The current stability data appeared acceptable from DMPQ perspective.