



Our STN: BL 125743/0

COMPLETE RESPONSE
February 25, 2022

Green Cross Corporation
Attention: (b) (4)

Dear (b) (4) :

Please refer to your Biologics License Application (BLA) submitted and received February 25, 2021, for immune globulin intravenous, human-stwk (ALYGLO) manufactured at your Cheongju-si, Chungcheongbuk-do, Republic of Korea 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 February 14, 2022. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

Chemistry, Manufacturing, and Controls

1. Based on the manufacturing activities observed, the translated documents reviewed, and the interviews of Green Cross Corporation (GCC) personnel during the Remote Interactive Evaluation (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 will be necessary to support approval of the subject application.

We acknowledge the responses to the deficiencies that were submitted by the 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.

Labeling

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

Post-Marketing Requirements

If this application is approved, you will be required to conduct post-marketing studies under Pediatric Research Equity Act (PREA) to obtain additional information that would clarify the issues of safety and effectiveness of ALYGLO in the pediatric population as follows:

- a. While we note that you have studied adolescents as per your Amended Agreed iPSP (initial pediatric study plan), there are insufficient pharmacokinetics (PK) data to (b) (4). Under PREA, you are required to conduct a new study to evaluate the PK, safety, and efficacy of ALYGLO in adolescents between ≥ 12 to < 17 years of age. The study should provide pharmacokinetic data for at least 6 subjects ages ≥ 12 to < 17 years old, as well as 12-month safety and efficacy data for these same subjects.
- b. We remind you that, per your Amended Agreed iPSP, there is a Post-Marketing Requirement (under PREA) to conduct a PK, safety, and efficacy study evaluating ALYGLO in children (age group ≥ 2 - < 12 years) per your Amended Agreed iPSP revised on February 4, 2021, and agreed to on February 9, 2021. The study should provide pharmacokinetic data for at least 6 subjects ages ≥ 2 to < 6 years old, as well as safety and efficacy data for these same subjects. The study should also provide PK data for at least 6 subjects ages ≥ 6 to < 12 years old, as well as safety and efficacy data for these same subjects.

Please describe your plans to address the above issues in sufficient detail to permit us to evaluate the adequacy of your proposals. Please provide the following information:

- A detailed outline describing all design features of each study, including sample size and justification, eligibility criteria with rationale, dosing regimens and duration, clinical assessments to be performed and their timing, and endpoints to be analyzed.
- A proposed schedule for conducting each study, including all major milestones for the study, e.g., submission date of the final protocol, completion date of the study, and submission date of the final study report.

Any additional specific details of this required post-marketing study, including a timetable and annual reporting requirements, will be described more fully in the approval letter for this application, if it is approved.

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 the guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf>, and 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>.

The deficiencies described above were the basis for not granting approval. We recommend, but do not require, that your complete response address the following additional concerns.

1. Your current risk assessment on Transmissible Spongiform Encephalopathies (TSE) is insufficient. Please conduct a risk assessment to estimate TSE agent removal by your manufacturing process. In addition to citing relevant literature, please identify steps in your process which have the potential to remove the TSE agent.
2. The (b) (4) content of product intermediates, (b) (4) and (b) (4), affects the properties of the (b) (4), including that of immune globulin G, during the (b) (4) process. Therefore, to ensure consistent manufacture of product intermediates, please monitor the (b) (4) content of the above-mentioned (b) (4) for at least (b) (4) lots.
3. The final process validation report is incomplete. It does not contain an evaluation of the lots manufactured under worst-case conditions, i.e., the engineering lots and lot (b) (4). The report should contain lots (b) (4), as well as the evaluation of critical process parameters, in-process controls, in-process specifications, and impurities. Please update your impurity profile analysis to include lots (b) (4). Following this analysis, please re-evaluate your Drug Product specifications.
4. Your (b) (4) study under the conditions of (b) (4) is incomplete. Please provide data indicating the

evaluation of samples taken at (b) (4) (b) (4)
(b) (4) at (b) (4) (b) (4) process of lot (b) (4) .

If you have any questions regarding the above, please contact the Regulatory Project Manager, Nancy Skeeter, at (240) 402-5427.

Sincerely,

Basil Golding, MD
Director
Division of Plasma Protein Therapeutics
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research