



Our STN: BL 125743/0

**LATE-CYCLE
MEETING MEMORANDUM**

December 30, 2021

Green Cross Corporation

Attention: (b) (4)

Dear (b) (4) :

Attached is a copy of the memorandum summarizing your November 30, 2021 Late-Cycle Meeting teleconference with CBER. This memorandum constitutes the official record of the meeting [teleconference]. If your understanding of the teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER in writing as soon as possible.

Please include a reference to Submission Tracking Number BL 125743/0 in future submissions related to the subject product.

If you have any questions, please contact Nancy Skeeter at nancy.skeeter@fda.hhs.gov.

Sincerely,

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

Late-Cycle Meeting Summary

Meeting Date and Time: November 30, 2021, 3:00-4:30 PM EDT
Meeting Location: Teleconference
Application Number: BLA 125743
Product Name: Immune Globulin Intravenous, Human-stwk, 10% Liquid
Proposed Indications: For the treatment of primary humoral immunodeficiency (PI)
Applicant Name: Green Cross Corporation
Meeting Chair: Michael Kennedy, PhD
Meeting Recorder: Nancy Skeeter, MBA

FDA ATTENDEES

Rachael Anatol, PhD, CBER/OTAT
Kimberly Benton, PhD, CBER/OTAT
Melanie Blank, MD, CBER/OTAT/DCEPT
Wilson W. Bryan, MD, CBER/OTAT
Dennis Cato, CBER/OCBQ/DIS/BMB
Lu Deng, PhD, CBER/OTAT/DPPT/PDB
Parmesh Dutt, CBER/OCBQ/DBSQC
Nancy Eller, MS, CBER/OTAT/DPPT/PDB
Mahmood Farshid, PhD, CBER/OTAT/DPPT
Varsha Garnepudi, MS, CBER/OCBQ/DBSQC
Basil Golding, MD, CBER/OTAT/DPPT
Christine Harman, PhD, OCBQ/DMPQ
Elizabeth Hart, MD, CBER/OTAT/DCEPT
Jie He, CBER/OCBQ/DMPQ
Lin Huo, PhD, CBER/OBE/DB
Michael Kennedy, PhD, CBER/OTAT/DPPT/PDB
Hyesuk Kong, CBER/OCBQ/DBSQC
Lily Koo, PhD, CBER/OCBQ/DMPQ
Vijay Kumar, MD, CBER/OTAT/DCEPT
Sarah Lee, CBER/OCBQ/DMPQ/ARB
Wei Liang, PhD, CBER/OTAT
Anthony Lorenzo, CBER/OCBQ/DMPQ
Xiuju (Sue) Lu, PhD, CBER/OCBQ/DMPQ
Tao Pan, PhD, CBER/OCBQ/DBSQC
Tejashri Purohit-Sheth, MD, CBER/OTAT/DCEPT
Carolyn Renshaw, CBER/OCBQ/DMPQ
Sonny Saini, CBER/OCBQ/DCM/APLB
Dorothy Scott, MD, CBER/OTAT/DPPT/PDB
Olga Simakova, PhD CBER/OTAT/DPPT/PDB
Ramani Sista, PhD, CBER/OTAT/DRPM
Nancy Skeeter, MBA, CBER/OTAT/DRPM
Lisa Stockbridge, PhD, CBER/OCBQ/DCM/APLB
Million Tegenge, PhD, CBER/OTAT/DCEPT
Alisha Thomas, MD, MPH, CBER/OTAT/OBE

Lori Tull, CBER/OTAT/DRPM
Maria Luisa Virata, PhD, CBER/OTAT/DPPT/PDB
Julia Wright, RN, MHA, CBER/OTAT/DRPM
Emnet Yitbarek, PhD, CBER/OCBQ/DBSQC
Boris Zaslavsky, PhD, CBER/OBE/DB

APPLICANT ATTENDEES

(b) (4), Project Leader for GCC 10% IGIV
(b) (4), Consultant
(b) (4), Consultant
Jaesun Kang, Clinical Manager
Chin Kim, Head of R&D
Jae Woo Lee, director of Development
Sungsil Lee, Clinical Manager
Sookyoung Shin, director of Clinical Department
Sang Min Shin, Regulatory Affairs Manager
(b) (4), US Agent

BACKGROUND

BLA 125743/0 was submitted on February 25, 2021, for Immune Globulin Intravenous, Human-stwk, 10% Liquid [ALYGLO].

Proposed indication(s): For the treatment of primary humoral immunodeficiency (PI)

PDUFA goal date: February 25, 2022

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on November 19, 2021.

DISCUSSION

1. Discussion of Substantive Review Issues

Chemistry, Manufacturing, and Controls (CMC)

1. CMC related observations from the Remote Interactive Evaluation (RIE; please refer to item 10 under DMPQ section).

Meeting Discussion: Please refer to Question 10 for discussion.

2. Stability – 4°C stability data acceptable and would support a 2-year shelf-life, but at 25°C, there is increasing (b) (4) and decreasing anti-HBsAg levels. Additional stability data is needed.

Meeting Discussion: 18-month stability data submitted in SN0034. Test results from all stability studies remain within the acceptance criteria and the 95% confidence intervals do not cross over the acceptance criteria over the test period of 18-month.

3. PMCs – Submit ongoing leachable study results for final container.

Meeting Discussion: The leachable study results at 12 months will be submitted on December 3, 2021.

4. Additional IR(s) may be required if the expected documents are evaluated as inadequate upon review. This includes:

- a. Process validation under the conditions of (b) (4).
- b. Hold time studies of (b) (4).
- c. The most current Standard Operating Procedures (SOPs) if different from those used during PPQ manufacturing.
- d. SOP for Biological Product Deviation Reports (BPDRs) for U.S. products.

Meeting Discussion:

- a. In IR#25 (SN0033), GCC's committed to submit process validation under the conditions of (b) (4).

The process robustness study was performed with (b) (4) U.S. commercial (b) (4) manufactured during the Remote Interactive Evaluations (RIE) and all

the test results met the pre-defined acceptance criteria and the referenced conditions.

The report will be submitted on December 3, 2021.

- b. GCC has evaluated lot release testing results from the first US commercial-scale drug product manufactured using approximately (b) (4). The following were evaluated according to the (b) (4) lifetime validation protocol and all the results met the predetermined acceptance criteria. Based on the results, GCC has set the conservative maximum hold times for the (b) (4)

- Process parameters (including (b) (4))
- Quality attributes
- Sanitization and cleaning efficiency
- Lot-to-lot product carryover
- Storage (hold) conditions

The hold time studies of (b) (4) will be submitted on December 3, 2021.

- c. GCC has reviewed total of 224 SOPs which were submitted to the FDA for preparation of Remote Interactive Evaluation. As a result of the review, GCC found 20 of 224 SOPs that were different from those used during PPQ manufacturing. The most current version of 20 SOPs will be submitted by December 9, 2021.
- d. The BPDR SOP will be prepared based on the following strategies and references.
- Procedure- Reportable deviations will be determined based on impact assessment for all internal and external events utilizing BPDR committee; The deviations classified as reportable will be reported to FDA within 45 days from the date of discovery of information.
 - Scope- Reportable Deviations: Deviations related to distributed batches or deviations may affect the safety, purity or potency of distributed batches; Adverse events will not be handled in this SOP, and will be reported through separate procedure
 - Reporting- BPD will be reported utilizing Form FDA 3486 in accordance with FDA's instructions; Licensed Non-Blood BPD Code will be given to each deviation

Clinical/Clinical Pharmacology:

5. Based on our review, there are insufficient pharmacokinetic data in (b) (4)
(b) (4)

Meeting Discussion: The Applicant asked for the Agency to clarify their comments on the individual (b) (4) data. The Applicant expressed their opinion that because the submitted PK data in (b) (4) subjects are complete except (b) (4)

FDA discussed the deficiencies of the available PK data. For adult subjects, more PK data are available from 28-days infusion group. FDA relied on the combined PK data from the 21- and 28-days infusion group for adult subjects; however, PK data are not available for (b) (4) subjects in (b) (4)

6. (b) (4), under section 505B (21 U.S.C. 355B) of the Federal Food, Drug, and Cosmetic Act [Pediatric Research Equity Act (PREA)], you will be subject to Post Marketing Requirements (PMRs) for PK, safety, and efficacy data in children 2-12 years and 12-17 years.

Meeting Discussion: The Applicant acknowledged that there would be a PREA PMR requiring them to collect more data in the 2-12 years age range. For children 12-17 years of age, more PK will be needed to inform dosing/ labeling. The applicant asked if there will be an additional PMR in the adolescent age group. FDA stated that the indication in the label will reflect the Agency's conclusions based on the available study data. If no adequate PK data are available to evaluate efficacy, that will have to be reflected in the label, and a subsequent PMR will be required for the age group 12-17 years old.

DMPQ:

7. The Remote Interactive Evaluation (RIE) observation memo was issued to GCC on November 16, 2021. GCC's response to the RIE observations is expected by December 9, 2021 (15 business days). The outcome of the RIE is pending review of the responses to the observations.

Meeting Discussion: The responses to the RIE observation memo will be submitted on December 9, 2021. Immediate actions will be implemented as soon as possible. The comprehensive, global corrective and preventive actions (CAPAs) will take more time, possibly extending past the PDUFA goal date (February 2022). GCC will report the progress to the Agency in regular intervals for the CAPAs.

The agency stated that the requirement for an on-site inspection will be determined upon reviewing GCC's response to the RIE observation memo.

8. The following are to be submitted to the BLA as amendments:

- a. Summary qualification report for the Ochang facility (b) (4)
- b. Study reports for the 10% IGIV product to support the adequacy of labeling/packaging for the U.S. product.

Meeting Discussion: Study report for the Labeling/Packaging System will be submitted on December 17, 2021.

- Labeling/packaging equipment were qualified with non-U.S. products.
- Labeling/packaging simulation with 10% IGIV 50 mL and 200 mL was performed last year.
- Based on the above the information, the study report will be prepared including the following.
 - Qualification information with non-U.S. products
 - Simulation condition with U.S. product (line speed, font size, bar-code and printing location, material size, etc.)
 - Comparison between simulation and actual manufacturing condition for U.S. product
- In the study report, it will be demonstrated that the U.S. product can be applied to the current labeling/packaging equipment.

2. Discussion of Minor Review Issues

At the time of the meeting, the review teams have not identified a need to discuss any minor review issues.

3. Additional Applicant Data

Meeting Discussion: Four analytical method changes were implemented after PPQ lots, without any impact on product quality. The changed SOPs will be submitted on December 3, 2021.

4. Information Requests:

At the time of the meeting, the review teams have not identified a need to discuss any information requests.

5. Postmarketing Requirements/Postmarketing Commitments

- a. Clinical: PREA - PMR(s): A PMR for children (age 2-<12), a PMR for adolescent age group (≥ 12 – <17 years old).
- b. Pharmacology/Toxicology and CMC: PMC for leachable studies to be concluded in 2022

6. Major Labeling Issues

Meeting Discussion: The clinical reviewer stated that the label would reflect the Agency's conclusions regarding the population(s) in whom efficacy/safety have been demonstrated and in whom there are sufficient PK data to inform dosing.

Another issue was raised regarding label expiry dating. Sponsor expressed that 24-month data will be submitted in January.

7. Review Plans

Meeting Discussion: Data and information will be sent in for December and January submissions.

8. Applicant Questions-

Meeting Discussion: GCC inquired about what the potential impact might be on the PDUFA goal date if they submitted more data in the December/January time range. The Agency responded that, depending on the size and complexity of the data submission, a major amendment might be triggered, which could possibly extend the review clock.

9. Wrap-up and Action Items

Meeting Discussion: The Agency stated that the BLA submission and reviews have not been fully reviewed by the signatory authorities, Division Directors and Review Committee Chair nor has the final regulatory decision been made.

The Agency agreed to complete a meeting summary in 30 days from the meeting.