



Our STN: BL 125810/0

**LATE-CYCLE
MEETING MEMORANDUM**

Biotest AG
Attention: Nina Tkachenko Carmichael
(b) (6)

Dear Nina Tkachenko Carmichael:

Attached is a copy of the memorandum summarizing your March 14, 2024, Late-Cycle Meeting with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the meeting 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 the appropriate Submission Tracking Number STN# BLA 125810 in future submissions related to the subject product.

If you have any questions, please contact Mona Badawy at Mona.Badawy@fda.hhs.gov.

Sincerely,

Mara Miller, MA
Director
Division of Review Management and Regulatory Review 2
Office of Review Management and Regulatory Review
Office of Therapeutic Products
Center for Biologics Evaluation and Research

Late-Cycle Meeting Summary

Meeting Date and Time: March 14, 2024, 11:00 AM-12:00 PM ET
Meeting Location: White Oak Building 71, Room 1208

Application Number: BLA 125810
Product Name: Immune Globulin Intravenous (Human)
Proposed Indications: For primary humoral immunodeficiency (PI) patients 2 years of age and older
Applicant Name: Biotest AG

Meeting Chair: Jennifer Reed, PhD
Meeting Recorder: Mona Badawy

FDA ATTENDEES

Afsah Amin, MD, MPH, CBER/OTP/OCE
Rachael Anatol, PhD, CBER/OTP
Mona Badawy, CBER/OTP/ORMRR
Hawa Camara, MS, PMP, CBER/OTP/ORMRR
Neetu Dahiya, PhD, CBER/OCBQ/DMPQ
Lu Deng, PhD, CBER/OTP/OPPT
Shelby Elenburg, MD, CBER/OTP/OCE
Mahmood Farshid, PhD, CBER/OTP/OPPT
Lola Fashoyin-Aje, MD, MPH, CBER/OTP/OCE
Basil Golding, MD, CBER/OTP/OPPT
Elizabeth Hart, MD, CBER/OTP/OCE
Kathleen Jones, PhD, CBER/OCBQ/DMPQ
Michael Kennedy, PhD, CBER/OTP/OPPT
Yeowon Kim, MD, MHS, CBER/OBPV/DPV
Wei Liang, PhD, CBER/OTP
Adamma Mba-Jonas, MD, MPH CBER/OBPV/DPV/PB
Leyish Minie, MSN, RN, CBER/OTP/ORMRR
Miriam Ngundi, PhD, CBER/OCBQ/DMPQ
Leonid Parunov, PhD, CBER/OTP/OPPT
Jennifer Reed, PhD, CBER/OTP/OPPT
Carolyn Renshaw, CBER/OCBQ/DMPQ
Dorothy Scott, MD, CBER/OTP/OPPT
Ramani Sista, PhD, CBER/OTP/ORMRR
Hairong (Helen) Shi, PhD, CBER/OBPV/DB
Edward Thompson, CBER/OTP/ORMRR
Nicole Verdun, MD, CBER/OTP
Maria Luisa Virata, PhD, CBER/OTP/OPPT
Pei Zhang, MD, CBER/OTP/OPPT

APPLICANT ATTENDEES

Silke Aigner, PhD, Sen. Director Corporate Clinical Strategy and Development

Marcel Asper, PhD Director Virus Laboratory Pathogen Safety

Reto Bisaz, PhD, Sen. Manager Corporate Regulatory Affairs

Julia Büllsbach, Manager Corporate Regulatory Affairs

Josefine Buth, Head Corporate Regulatory Affairs

Nina Carmichael, US Agent for Biotest AG

(b) (6) PhD, Head Quality Control

(b) (6) , PhD, Head Preclinical Research

(b) (6) PhD, Head Production 1, 2 and 3

(b) (6) Head Quality Assurance Systems

(b) (6) PhD, Head Analytical Development and Validation

(b) (6) Head Production 3

(b) (6) PhD, Head Validation Production 3

(b) (6) , PhD, Head External Development

(b) (6) Medical Safety Advisor

(b) (6) PhD, Head of Development

(b) (6) Head Production 1

Frank Morfeld, PhD, Sen. Director CMC Management Plasma Proteins

(b) (6) PhD, Head Production 2

Christine Piasek, Director Corporate Regulatory Affairs

Gerhard Poelsler, PhD, Sen. Director Pathogen Safety

(b) (6) PhD, Head Validation Production 2

(b) (6) Head Corporate Drug Safety

Katrin Schulze, PhD, Manager Quality Assurance Systems Inspection
Management

Jörg Schüttrumpf, PhD, Chief Scientific Innovation Officer

(b) (6) Head Corporate Quality Operations

Kelly Smith, Senior Director of Regulatory Affairs

Christiane Staiger, PhD, Sen. Manager Corporate Clinical Research and
Development

(b) (6) PhD Medical Safety Advisor

(b) (6) Head Quality Assurance Operations

(b) (6) PhD Project Leader Development & LC-Projects

Yuan Zhao, PhD, Manager Corporate Regulatory Affairs

BACKGROUND

BLA 125810/0 was submitted on June 30, 2023, for Immune Globulin Intravenous (Human).

Proposed indication: For the treatment of primary humoral immunodeficiency (PI) in patients 2 years of age and older

PDUFA goal date: June 29, 2024

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on March 5, 2024.

DISCUSSION

1. Discussion of Substantive Review Issues

Each issue was introduced by FDA and it was followed by discussions.

Chemistry, Manufacturing and Controls:

- a. Repeat occurrence of (b) (4) (b) (4) AEX step since May 21, 2023 – no definitive root cause identified, pending final product impact analysis report.

Meeting discussion:

FDA requested for Biotest to provide additional data confirming root cause and corrective actions as soon as possible, including sampling justification, and to justify the LOQ in the obtained data. Information will be provided as a response to FDA information request.

- b. At least one commercial lot with minimum batch size using U.S. Source Plasma.

Meeting discussion:

FDA informed Biotest that manufacturing data from the (b) (4) PPQ lots manufactured on the dedicated U.S. line using U.S. source plasma were acceptable (with minor modifications). The FDA agreed that Biotest can update the BLA back to the PPQ levels through a formal information request.

- c. Maximum permissible in-process (b) (4) process times study using U.S. Source Plasma.

Meeting discussion:

Additional validation data supporting maximum processing times, minimal batch size, and use of (b) (4) are still required. To ensure efficiency, FDA recommended use of a prospective comparability protocol to be submitted and reviewed as a prior-approval supplement (PAS) after the initial BLA approval. FDA agreed to provide feedback on Biotest's strategy for supporting commercial manufacture with maximum processing times, minimal batch size and use of (b) (4) potentially to include a meeting for additional discussion if needed.

- d. At least one commercial lot using (b) (4) after maximum allowable storage time.

Meeting discussion:

See discussion under c.

- e. (b) (4) using commercial scale (b) (4)
(b) (4) manufactured with U.S. Source Plasma.

Meeting discussion:

FDA confirmed that the provided validation data set should (b) (4) maximum and minimum volumes as worst case.

Clinical:

- f. Determination of whether infections during the clinical trial constitute serious bacterial infections (SBI).

Meeting Discussion:

FDA clarified that the Applicant's responses to the recent information request regarding infections are under review. FDA is in the process of adjudicating events and re-calculating the SBI rates. The Applicant clarified that, in providing responses to the information request, investigators were queried about adjudication of infectious events in determining whether certain infections qualified as SBIs, which were defined according to the FDA Guidance. FDA stated that the review team will contact the Applicant if additional information is needed.

- g. Interpretation of IgG trough levels in the setting of dose changes (both planned and actual) and reported infections.

Meeting Discussion:

FDA indicated that information request responses related to dose changes are still under review. The Applicant clarified that no dose changes were due to SBIs; dose changes attributed to low IgG were either performed at the investigator's discretion or for IgG troughs below 5g/L. FDA stated that their analysis would include subject-level analysis comparing IgG trough levels during the trial to their baseline level.

- h. Hemolytic events after the product administration have been identified as a safety signal.

Meeting Discussion:

FDA discussed that hemolysis after product administration has been identified as a safety signal. FDA acknowledged that hemolysis was limited to changes in laboratory parameters in study 991. The Applicant clarified that no transfusions were required for hemolytic events in either Study 991 or Study 992. The Applicant also clarified that post-marketing reports in Austria and Germany indicate no reports of hemolysis in patients with PID, and one event

of hemolysis reported following treatment in a patient with MMN treated with a higher dose of product than doses administered for PID in study 991.

- i. Analysis of PK and safety in children between 2-5 years.

Meeting Discussion:

FDA stated that the review team was still considering whether data on three subjects in the 2-5 years age group are sufficient to inform dosing, safety, and efficacy in this youngest pediatric population. The Applicant discussed PK modeling and extrapolation from the modeling supported the analysis of no difference between the different age groups and the FDA acknowledged that both were under review.

2. Additional Applicant Data

No discussion occurred.

3. Information Requests

Currently, there are no pending IRs. As our review continues, new information requests will be conveyed as needed.

4. Risk Management Actions (e.g., REMS, the ability of adverse event reporting and CBER's Sentinel Program to provide sufficient information about product risk)

The review is ongoing. At this time, we have not identified any issues related to risk management and do not believe that a REMS will be required.

5. Postmarketing Requirements/Postmarketing Commitments

The review is ongoing. Currently, the need for PMRs or PMCs remains undetermined.

6. Major Labeling Issues

Label review is ongoing. Labeling issues will be discussed during the labeling negotiations.

7. Review Plans

- a. PMRs will be communicated no later than May 4, 2024, if needed
- b. PMCs will be communicated no later than May 30, 2024, if needed
- c. Label will be sent to Applicant for negotiations no later than May 30, 2024.

8. Applicant Questions

Meeting Discussion:

Biotest inquired about whether their current validation approach for the (b) (4) is acceptable. The FDA responded that the review of the submitted validation strategy and the data from interim reports is still ongoing. The FDA's comment to Biotest on February 14, 2024, stated what is typically required for a (b) (4) study. The data from the clinical manufacturing plant can be used as supporting data; a (b) (4) (b) (4) study might be needed to support proposed maximum (b) (4) (b) (4) pending the final review of the submitted data. Concurrent validation for (b) (4) and (b) (4) (b) (4) (b) (4) is acceptable. A detailed proposal for the concurrent validation concept should be provided and discussed with the FDA.

Biotest inquired about why using the clinical (b) (4) material from (b) (4) process to validate commercial scale (b) (4) are not acceptable. The FDA responded that commercial scale (b) (4) materials are typically required to make sure all (b) (4) work properly and have no negative impact on the final drug product that will be marketed in U.S. The FDA also recommended a (b) (4) approach to validate (b) (4) of different sizes, using minimum and maximum batch size, and preferably also using routine batch size.

Biotest inquired about whether a decision on the pre-license inspection has been made and when the EIR would be available. The FDA responded that the inspection has not been closed. The final decision has not been made as the FDA is still reviewing the responses to request of additional information. The date when the EIR would be available could not be provided at this time.

9. Wrap-up and Action Items

FDA reiterated that PMRs will be communicated to the Applicant no later than May 4, 2024, and PMCs will be communicated no later than May 30, 2024. The label will be sent to the Applicant for negotiations by May 30, 2024. The FDA confirmed the meeting summary will be provided to Biotest AG within 30 days.

This application has not yet been fully reviewed by the signatory authorities, Division Directors, and Review Committee Chair and therefore, this meeting did not address the final regulatory decision for the application.

END