Our STN: BL 125810/0

BLA APPROVAL
June 13, 2024

Biotest AG
Attention: Peter Janssen
Landsteinerstrasse 5
Dreieich, Hesse 63303
Germany

Dear Peter Janssen:

Please refer to your Biologics License Application (BLA) received June 30, 2023, submitted under section 351(a) of the Public Health Service Act (PHS Act) for immune globulin intravenous, human-dira.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2332 to Biotest AG, Dreieich, Germany, under the provisions of section 351(a) of the PHS Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product immune globulin intravenous, human-dira, which is indicated for the treatment of primary humoral immunodeficiency (PI) in patients 2 years of age or older.

The review of this product was associated with the following National Clinical Trial (NCT) number: 02810444.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture immune globulin intravenous, human-dira at your facility located at Dreieich, Germany. You may label your product with the proprietary name YIMMUGO and market in type (b)(4) glass vials of 50, 100, or 200 mL volumes.

ADVISORY COMMITTEE

We did not refer your application to Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results,

did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

DATING PERIOD

The dating period for immune globulin intravenous, human-dira shall be 30 months from the date of manufacture when stored at 5°C ± 3°C with a one-time period of storage up to six months at NMT 25°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency.

FDA LOT RELEASE

Please submit final container samples of the product in final containers together with protocols showing results of all applicable tests. You may not distribute any lots of the product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to the Director, Office of Compliance and Biologics Quality, electronically through the eBPDR web application or at the address below. Links for the instructions on completing the electronic form (eBPDR) may be found on CBER's web site at https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviations :

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of immune globulin intravenous, human-dira, or in the manufacturing facilities.

LABELING

We hereby approve the draft content of labeling including Package Insert, submitted under amendment 106, dated June 12, 2024, and the draft package and container labels submitted under amendment 106, dated June 12, 2024.

WAIVER OF HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system, (eLIST) as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the Package Insert submitted on June 12, 2024. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

PACKAGE AND CONTAINER LABELS

Please electronically submit final printed package and container labels identical to the package and container labels submitted on June 12, 2024 according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf.

All final labeling should be submitted as Product Correspondence to this BLA, STN BL 125810/0 at the time of use and include implementation information on Form FDA 356h.

ADVERTISING AND PROMOTIONAL LABELING

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. In addition to the reporting requirements in 21 CFR 600.80, you must submit adverse experience reports for all adverse events involving hemolysis, regardless of label status or seriousness, as 15-day expedited reports to the FDA Adverse Event Reporting System (FAERS). Adverse experience reports of hemolysis must be submitted as 15-day expedited reports for 3 years following the date of product licensure. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-submissions-electronic-format-postmarketing-safety-reports and FDA's Adverse Event reporting System website at https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at https://www.fda.gov/vaccines-blood-biologics/lot-release/lot-distribution-database-ldd.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or

new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages from birth to less than 2 years of age because the necessary studies are impossible or highly impracticable. This is because the number of patients diagnosed with primary humoral immunodeficiency in this age group is so small.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitments as described in your letter of May 20, 2024 as outlined below:

1. Biotest commits to completing implementation of (b) (4) sampling and testing as indicated in Amendment STN 125810/0.47, before production of the first commercial U.S. YIMMUGO lot, and to submit the related change controls in the first Annual Report by August 31, 2025.

   Final Report Submission: August 31, 2025

2. Biotest commits to completing (b) (4) evaluations with effective (b) (4) for samples (b) (4) the YIMMUGO (b) (4) (b) (4) and to submitting the study report as a Postmarketing Commitment Submission - Final Study Report by June 30, 2025.

   Final Report Submission: June 30, 2025

3. Biotest commits to completing a (b) (4) validation study for (b) (4) which is used for the drug substance (b) (4) and to submit the final validation study report as a Changes Being Effected (CBE) supplement by November 30, 2024. Biotest also commits to place the lot processed with the maximum (b) (4) (b) (4) on stability. Interim stability data will be submitted annually as a Postmarketing Commitment Submission – Status Update. A final stability study report will be submitted by May 31, 2027, as a Postmarketing Submission – Final Study Report. Any stability failures will be reported within 45 days of the occurrence as a Postmarketing Commitment Submission – Status Update.

   Changes Being Effected (CBE) Supplement Submission: November 30, 2024

   Final Validation Report Submission: November 30, 2024

   Final Stability Report Submission: May 31, 2027

4. Biotest commits to performing concurrent (b) (4) validation studies for the (b) (4) at Step (b) (4) and Step (b) (4) respectively. The interim results of the studies will be submitted annually in the Annual Report. The final validation study reports will be submitted as a Changes Being Effected (CBE) supplement no later than June 30, 2026. Biotest commits to notifying the FDA of any (b) (4) failures within 45 days of the occurrence as a Postmarketing Commitment Submission - Status Update.

   Changes Being Effected (CBE) Supplement Submission: June 30, 2026

5. Biotest commits to performing a concurrent (b) (4) validation study for the (b) (4) Interim results will be submitted annually in the Annual Report. The final validation study report will be submitted as a Changes Being Effected (CBE) supplement not later than June 30, 2026. Biotest commits to notifying the FDA of any (b) (4) failures within 45 days of the occurrence as a Postmarketing Commitment Submission - Status Update.

   Changes Being Effected (CBE) Supplement Submission: June 30, 2026

6. Biotest commits to submitting a validation study final report to confirm the proposed maximum (b) (4) for the (b) (4) as a Changes Being Effected (CBE) supplement by June 30, 2026. Biotest commits to notifying the FDA of any (b) (4) failures within 45 days of the occurrence as a Postmarketing Commitment Submission - Status Update.

   Changes Being Effected (CBE) Supplement Submission: June 30, 2026

7. Biotest commits to implementing the (b) (4) test for Drug Product lot release and setting the specification based on Drug Product testing results. Biotest commits to submitting the corresponding (b) (4) method SOP and the final validation study report for testing DP will be submitted as a Prior Approval Supplement (PAS) no later than September 30, 2024. In the interim, Biotest commits to testing for (b) (4) in the (b) (4) with a specified limit of (b) (4) until the PAS is approved.

   Prior Approval Supplement (PAS) Submission: September 30, 2024

8. Biotest commits to performing a (b) (4) study to support product (b) (4) during (b) (4) for the (b) (4) and to submit the study report as a Postmarketing Commitment Submission - Final Study Report by August 31, 2024.

   Final Report Submission: August 31, 2024

9. Biotest commits to performing a complete virus clearance validation study for the (b) (4) step with a (b) (4) range from (b) (4) and conducting a

robustness study with a (b) (4) greater than (b) (4) using the (b) (4) collected from commercial scale production of YIMMUGO as testing materials. Biotest commits to submit the final study reports will be submitted as a Changes Being Effected (CBE) supplement no later than October 31, 2024.

Changes Being Effected (CBE) Supplement Submission: October 31, 2024

10. Biotest commits to providing the complete stability data supporting BT595 PPQ drug product batches manufactured from US plasma in study BE-Q-301j-95 as a Postmarketing Commitment Submission – Final Study Report by December 31, 2024.

    Final Report Submission: December 31, 2024

11. Biotest commits to providing the complete leachables data supporting BT595 PPQ drug product batches manufactured from US plasma in study BE-186-95 as a Postmarketing Commitment Submission – Final Study Report by December 31, 2024.

    Final Report Submission: December 31, 2024

12. Biotest commits to providing the final CAPA report for 200195300 as a Postmarketing Commitment Submission – Final Study Report by November 30, 2024.

    Final Report Submission: November 30, 2024

We request that you submit information concerning chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA, STN BL 125810/0. Please refer to the sequential number for each commitment.

Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Status Update**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing commitment not subject to the reporting requirements of 21 CFR 601.70, you may report the status to FDA as a **Postmarketing Commitment – Status Update**. The status report for each commitment should include:

- the sequential number for each study as shown in this letter;
- the submission number associated with this letter;
- describe what has been accomplished to fulfill the non-section 506B PMC; and,
- summarize any data collected or issues with fulfilling the non-section 506B PMC.

When you have fulfilled your commitment, submit your final report as **Postmarketing Commitment – Final Study Report** or **Supplement contains Postmarketing Commitment – Final Study Report**.

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

Sincerely,

Melissa Mendoza, JD
Director
Office of Compliance
and Biologics Quality
Center for Biologics
Evaluation and Research

Sincerely,

Lola Fashoyin-Aje, MD, MPH
Director
Office of Clinical Evaluation
Office of Therapeutic Products
Center for Biologics
Evaluation and Research