
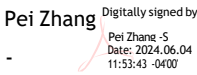




Memorandum

To: File BLA STN 125810/0

From: Lu Deng, OTP/OPPT/DPD/PDB2  Digitally signed by Lu Deng -S
Date: 2024.06.04 11:40:37 -0400

Pei Zhang, OTP/OPPT/DPD/PDB2  Digitally signed by Pei Zhang -S
Date: 2024.06.04 11:53:43 -0400

Through: Jennifer Reed, Branch Chief, OTP/OPPT/DPD/PDB2
Dorothy Scott, Division Director, OTP/OPPT/DPD

CC: Mona Badawy, RPM, OTP/ORMRR

Applicant: Biotest AG

Product: Immune Globulin Intravenous (Human), 10% Liquid
Trade name: Yimmugo

Subject: Original BLA CMC Final Review: **Process Validation, Control of Materials, Controls of Critical Steps and Intermediates, Pre-License Inspection, and Viral Clearance Validation**

Recommendation

Approval with the following Postmarketing Commitments (PMCs):

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

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 Effectuated (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.
5. Biotest commits to performing a concurrent (b) (4) validation study for the (b) (4) (b) (4). Interim results will be submitted annually in the Annual Report. The final validation study report will be submitted as a Changes Being Effectuated (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.
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 Effectuated (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.
7. Biotest commits to performing a (b) (4) study to support product (b) (4) during (b) (4) (b) (4) for the (b) (4) and to submit the study report as a Postmarketing Commitment Submission - Final Study Report by August 31, 2024.
8. 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. The final study reports will be submitted as a Changes Being Effectuated (CBE) supplement no later than October 31, 2024.

Executive Summary

Yimmugo is a ready-to-use, sterile liquid preparation of concentrated human immunoglobulin G (IgG) antibodies indicated for the treatment of primary humoral immune deficiency. It is prepared from plasma donated by healthy qualified plasma donors. The plasma is processed to (b) (4) according to the (b) (4) cold alcohol fractionation process, then precipitated by caprylic acid, and further purified by two chromatography steps. Virus inactivation and reduction is ensured by caprylic acid precipitation, low pH treatment, (b) (4) nanofiltration and anion-exchange chromatography.

The final product is formulated with (b) (4) glycine and (b) (4) polysorbate 80 and is filled in configurations of 50 mL, 100 mL, and 200 mL solution. The product is supplied in clear, colorless type (b) (4) glass bottles closed with bromobutyl type (b) (4) rubber stoppers and flanged with flip-off aluminum caps. Biotest proposes a shelf life of 30 months at 2-8 °C, and within its shelf-life, the product may be stored at 25 °C for up to 6 months.

The Biologics License Application (BLA) for Immune Globulin Intravenous (Human), 10% Liquid, Yimmugo from Biotest AG was received on June 30, 2023, and it received a standard 12-month review. The firm's internal name for Yimmugo is "IgG Next Generation (BT595)." This review memorandum covers the following assigned CMC sections of the original BLA submission.

- Process validation, control of materials, controls of critical steps and intermediates, pre-license inspection (Lu Deng)
- Viral clearance validation (Pei Zhang)

Submission Review

Description of Manufacturing Process

(b) (4)

5 pages have been determined to be not releasable: (b)(4)

(b) (4)

Control of Materials

Human Source Plasma is used as the starting material for Yimmugo. Recovered plasma is not used. Source Plasma is obtained from FDA licensed plasmapheresis centers. The plasma must conform to 21 CFR Part 640 subpart G. Plasma received from qualified suppliers is stored at (b) (4) or colder at an FDA approved off-site storage facility or at Biotest. Source plasma may be stored for a maximum of (b) (4) after donation. The procedures for inventory hold, traceability and lookback were checked during the on-site pre-license inspection. Each Source Plasma unit is tested and found negative for HBsAg, HIV-1/-2 antibody, and HCV antibody. A serological test for syphilis is also performed according to 21 CFR Part 640.65. The testing of plasma (b) (4) is performed prior to shipment of plasma to Biotest's FDA approved storage facility. Nucleic acid test (NAT) is performed for HIV, HBV, HCV, HAV and Parvovirus B19 at the manufacturing pool level.

The firm provided a copy of Certificates of Analysis (CoA) and a list of raw materials used for Yimmugo manufacturing including the information on suppliers, model numbers and catalog numbers. (b) (4) methods are used for most of the raw materials testing. Biotest in-house tests are conducted for (b) (4) materials, such as (b) (4) (b) (4) Testing frequency of all raw materials depend on supplier status and the risk class of each material. A quality agreement or change notification commitment which specifies that Biotest will be informed in the event of any changes is in place with each supplier.

Viral Clearance Validation Studies

The manufacturing process of IgG Next Generation (BT595) contains four steps dedicated to remove/inactivate adventitious viruses to increase the margins of safety, including caprylic acid and low pH treatment, anion exchange chromatography (AEX) and nanofiltration. Virus clearance studies have been performed with a (b) (4) process for these steps to determine their capacity to

inactivate or remove both enveloped (HIV, BVDV, PRV) and non-enveloped (HAV, EMCV, B19V, PPV, HEV) viruses (Table 2). The supporting viral clearance study reports are listed in Appendix V.

Table 2: Virus Clearance Data (Log10) for YIMMUGO for lipid-enveloped (HIV, BVDV, PRV) and non-enveloped viruses (HAV, EMCV, B19V, PPV, HEV)

Virus/Step	HIV	BVDV	PRV	HAV	EMCV	B19V *	PPV	HEV *
Caprylic Acid Treatment	≥ 5.64	≥ 5.97	≥ 6.21	≥ 4.39	n.d.	2.48	1.01	≥ 4.96
Low pH Treatment	≥ 6.63	< 1	n.d.	n.d.	n.d.	n.d.	< 1	n.d.
Anion Exchange Chromatography	n.d.	2.62	n.d.	≥ 3.95	n.d.	≥ 5.86	3.21	n.d.
Virus Filtration	≥ 4.72	≥ 4.72	n.d.	≥ 4.37	≥ 4.93	≥ 4.33	6.12	n.d.
Total Virus Clearance †	≥ 16.99	≥ 13.31	≥ 6.21	≥ 12.71	≥ 4.93	≥ 12.67	10.34	≥ 4.96

n.d. not determined.

* Polymerase chain reaction (PCR) was used to quantify B19V and HEV genome counts (all other viruses were quantified by in-vitro infectivity assays, using mammalian cell lines).

† Log10 reduction factors of 1 or smaller were not considered for calculation of total virus clearance.

BVDV, bovine viral diarrhea virus, a model for hepatitis C virus; **PRV**, pseudorabies virus, a model for hepatitis B virus; **EMCV**, encephalomyocarditis virus, a model for hepatitis A virus; **B19V**, parvovirus B19; **PPV**, porcine parvovirus, a model for B19V; **HEV**, hepatitis E virus.

Inactivation of Viruses by Caprylic Acid (CA) Treatment

(b) (4)

(b) (4)

Inactivation of HIV by Low pH Treatment

(b) (4)

Removal of Virus by Anion Exchange Chromatography

(b) (4)

Viral Clearance by Nanofiltration (b) (4)

(b) (4)

(b) (4)

Pre-license Inspection Summary and Inspectional Follow-up

CBER conducted a pre-license inspection (PLI) of Biotest AG, located in Dreieich, Germany (FEI: 3001034985) December 4 – 8 & December 11 – 15, 2023. I (Lu Deng) conducted the inspection as a product specialist together with inspectors from the Office of Compliance and Biologics Quality. The PLI resulted in ten Observations and six Discussion Items. The CMC related observations are for inadequate quality oversight to assure that the Yimmugo drug product has the identity, strength, quality, and purity it purports or is represented to possess; deviation management is inadequate to demonstrate quality oversight of the manufacturing process, and does not adequately identify, document, or investigate the impact to drug product; procedures designed to monitor microbiological contamination are not established; process validation is deficient as it does not cover the proposed range for process parameters that are critical; and process controls are not established from validated manufacturing processes. The findings from the PLI resulted in four PMCs regarding (b) (4) monitoring, endotoxin testing, (b) (4) validation used for (b) (4) and viral clearance validation at (b) (4) (PMCs 1, 2, 3, 8). Please see the PLI Observation Memo, PLI Observation Response Memo and the PLI Establishment Inspection Report for detailed information including inspectional follow-up items.

Information Requests

The following is a list of amendments that the firm provided in response to CMC information requests. The responses are summarized in the above review sections.

STN 125810/0.1-3, 5-6, 9-12, 14, 16, 19, 23, 24, 26, 27, 29, 30, 32, 34, 41, 47, 48-49, 52-54, 59, 62, 65, 68, 71, 72, 75, 76, 79, 87, 88, 93, 96, 97 and 98.

Appendix I

Overview of Yimmugo (b) (4) manufacturing process (copied from eCTD 3.2.S.2.2
Description of Manufacturing Process and Process Controls)

(b) (4)

Appendix II

Overview of Yimmugo drug product manufacturing process (copied from eCTD 3.2.P.3.3
Description of Manufacturing Process and Process Controls)

(b) (4)

Appendix III

Critical parameters and specifications for (b) (4) manufacturing

(b) (4)

Appendix IV

Overview of PPQ Batches and Batch Numbers

(b) (4)

Appendix V

Virus clearance studies for the IgG Next Generation manufacturing process

Report No.	Year	Title
BE-T:E-003b-95	(b) (4)	
BE-T:E-003c-95		
BE-T:E-003d-95		
BE-T:E-003f-95		
BE-T:E-003h-95		
BE-T:E-003i-95		
BE-T:E-003k-95		
BE-137-95		
BE-153-95		
BE-158-95		
BE-166-95		
BE-171-95		