

**CBER DMPQ CMC/Facility BLA Review Memorandum**

**BLA STN 125810/0**

**Immune Globulin Intravenous (Human) 10% liquid; YIMMUGO; IgG Next  
Generation (BT595)**

**Miriam Ngundi, Consumer Safety Officer, OCBQ/DMPQ/MRB1  
Neetu Dahiya, Biological Reviewer, OCBQ/DMPQ/MRB1**

1. **BLA#:** STN 125810/0

2. **APPLICANT NAME AND LICENSE NUMBER**

Biotest AG; License No: 2332

3. **PRODUCT NAME/PRODUCT TYPE**

Non-proprietary/proper/USAN: Immune globulin intravenous (human)

Proprietary name: YIMMUGO

4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**

a. Pharmacological category: Human immunoglobulin G

b. Dose form: Solution for injection

c. Strength/Potency: 10% (100 mg/mL) solution for infusion containing at least 96% IgG with the four subclasses IgG1, IgG2, IgG3, IgG4 and a maximum of [REDACTED] IgA and [REDACTED] IgM molecules

d. Route of administration: Intravenous

e. Indication(s): Treatment of primary humoral immunodeficiency (PI) in patients 2 years of age or older

5. **MAJOR MILESTONES**

Filing action date: August 29, 2023

Facility inspection: December 04 – 08 and 11 – 15, 2023

Mid-cycle meeting with Biotest: January 4, 2024

Late-cycle meeting with Biotest: March 14, 2024

PDUFA action date: June 29, 2024

6. **DMPQ CMC/FACILITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Neetu Dahiya, OCBQ/DMPQ/MRB1	3.2.S Drug substance (DS) 3.2.A.1 Facilities and equipment for DS 3.2.R Regional Information (USA) Comparability Protocols
Miriam Ngundi OCBQ/DMPQ/MRB1	3.2.P Drug product (DP) 3.2.A.1 Facilities and equipment for DP

7. **SUBMISSION(S) REVIEWED**

Date Received	Submission	Comments/ Status
06/29/2023	STN 125810/0	Original submission / Reviewed
08/01/2023	Amendment STN 125810/0.1 Response to IR dated 07/26/2023	Lot release protocol / Reviewed
08/10/2023	Amendment STN 125810/0.3 Response to information request (IR) dated 08/28/2023	Manufacturers - Testing laboratories / Reviewed
08/18/2023	Amendment STN 125810/0.8 Response to IR dated 08/10/2023	Information to prepare for pre- license inspection / Reviewed

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Date Received	Submission	Comments/ Status
10/06/2023	Amendment STN 125810/0.15 Response to IR dated 09/15/2023	Records Request (704(a)(4)) / Reviewed
10/11/2023	Amendment STN 125810/0.17 Response to IR dated 09/15/2023	Records Request (704(a)(4)) / Reviewed
10/19/2023	Amendment STN 125810/0.20 Response to IR dated 09/15/2023	Records Request (704(a)(4)) / Reviewed
10/20/2023	Amendment STN 125810/0.21 Response to IR dated 10/06/2023	Facilities and Equipment / Reviewed
10/23/2023	Amendment STN 125810/0.22 Response to IR dated 09/15/2023	Records Request (704(a)(4)) / Reviewed
11/02/2023	Amendment STN 125810/0.25 Response to IR dated 10/06/2023	Facilities and Equipment / Reviewed
11/13/2023	Amendment STN 125810/0.28 Response to IR dated 10/06/2023	Facilities and Equipment / Reviewed
12/06/2023	Amendment STN 125810/0.31 Response to IR dated 11/08/2023	DP Manufacturing Process and Process Controls, and Process Validation and/or Evaluation / Reviewed
12/22/2023	Amendment STN 125810/0.38 Response to IR dated 12/20/2023	Change in the responsibility of the batch release from Biotest (b) (4) to Biotest AG / Reviewed
01/05/2024	Amendment STN 125810/0.41 Response to IR dated 12/21/2023	Contamination control in Building (b) (4) / Reviewed
01/10/2024	Amendment STN 125810/0.42 Response to Form FDA 483	PLI - Response to Form FDA 483 observations issued on 12/15/2023 / Reviewed
02/02/2024	Amendment STN 125810/0.47 Response to IR dated 01/18/2024	Bioburden sampling positions / Reviewed
02/05/2024	Amendment STN 125810/0.49 Response to IR dated 01/24/2024	Anion exchange (AEX) and cation exchange (CEX) (b) (4) studies / Reviewed
02/07/2024	Amendment STN 125810/0.50 Response to IR dated 01/24/2024	Updated stability data / Reviewed
02/08/2024	Amendment STN 125810/0.51 Response to IR dated 01/29/2024	Updated stability data / Reviewed
02/05/2024	Amendment STN 125810/0.52 Response to IR dated 01/26/2024	(b) (4) validation study / Reviewed
02/20/2024	Amendment STN 125810/0.55 Response to IR dated 02/05/2024	HVAC system, (b) (4) rooms and equipment qualification / Reviewed
02/23/2024	Amendment STN 125810/0.57 Response to IR dated 02/09/2024	Response to RAI for response to Form FDA 483 / Reviewed

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Date Received	Submission	Comments/ Status
02/26/2024	Amendment STN 125810/0.58 Response to IR dated 02/05/2024	Facility and equipment qualification / Reviewed
02/27/2024	Amendment STN 125810/0.59 Response to IR dated 02/05/2024	AEX/CEX storage times / Reviewed
02/29/2024	Amendment STN 125810/0.62 Response to IR dated 02/14/2024	PPQ data from US and non-US plasma / Reviewed
03/04/2024	Amendment STN 125810/0.63 Response to IR dated 02/16/2024	DP process validation, Facilities and Equipment / Reviewed
03/08/2024	Amendment STN 125810/0.65 Response to IR dated 02/29/2024	Update to remove (b) (4) of DP / Reviewed
03/08/2024	Amendment STN 125810/0.66 Response to IR dated 02/28/2024	Response to RAI for response to Form FDA 483 / Reviewed
03/11/2024	Amendment STN 125810/0.67 Response to IR dated 02/26/2024	Media fills, visual inspection, CCIT for stability and HVAC / Reviewed
04/04/2024	Amendment STN 125810/0.70 Response to IR dated 03/26/2024	Response to RAI for response to Form FDA 483 / Reviewed
04/09/2024	Amendment STN 125810/0.72 Response to IR dated 03/29/2024	Data from (b) (4) to support (b) (4)
04/11/2024	Amendment STN 125810/0.73 Follow up on IR dated 02/09/2024	Response to RAI for response to Form FDA 483 / Reviewed
04/19/2024	Amendment STN 125810/0.75 Response to IR dated 04/04/2024	Proposed process validation studies and removal from BLA the use of (b) (4) / Reviewed
04/24/2024	Amendment STN 125810/0.77 Follow up on IR dated 02/09/2024	Response to RAI for response to Form FDA 483 / Reviewed
04/30/2024	Amendment STN 125810/0.79 Response to IR dated 04/16/2024	Process control parameters and manufacturing ranges / Reviewed
05/06/2024	Amendment STN 125810/0.80 Response to IR dated 04/30/2024	(b) (4) validation, CCS, and DP stability testing / Reviewed
05/07/2024	Amendment STN 125810/0.83 Response to IR dated 05/01/2024	Clean and sanitized hold times / Reviewed
05/10/2024	Amendment STN 125810/0.85 Follow up on IR dated 05/01/2024	Protocols for clean and sanitized hold times validation / Reviewed
05/10/2024	Amendment STN 125810/0.86 Follow up on IR dated 05/01/2024	Response to RAI for response to Form FDA 483 / Reviewed
05/10/2024	Amendment STN 125810/0.87 Response to IRs dated 03/29/2024 and 04/03/2024	Update on process control parameters
05/10/2024	Amendment STN 125810/0.88 Response to IR dated 05/03/2024	Update on (b) (4) (b) (4) study protocol and

Date Received	Submission	Comments/ Status
		AEX/CEX (b) (4) studies, and Process control parameters / Reviewed

## 8. REVIEWER SUMMARY AND RECOMMENDATION

### A. EXECUTIVE SUMMARY

Biotest AG submitted Biologics License Application (BLA) STN 125810/0 to support the licensure of Immune globulin intravenous (human), YIMMUGO, a polyvalent human immunoglobulin solution for treatment of Primary humoral immunodeficiency (PI) in patients 2 years of age and older. YIMMUGO is manufactured at the Biotest AG facility located in Dreieich, Germany. The Office of Compliance and Biologics Quality, Division of Manufacturing and Product Quality (OCBQ/DMPQ) reviewed and evaluated the drug (b) (4) drug product (DP) manufacturing processes, facilities, and equipment proposed for the manufacture of YIMMUGO. This review memo includes summaries and assessments of the (b) (4) DP manufacturing process, quality attributes, facility information including utilities, cross-contamination controls, qualification and maintenance of classified environments and manufacturing equipment, cleaning and sanitization/sterilization processes, and types of equipment used (i.e., dedicated or shared, multi-use or single-use).

A records request was made in advance of a pre-license inspection (PLI) of the Biotest AG facility (Dreieich, Germany) according to section 704(a)(4) of the FD&C Act. Items identified to be of concern during the manufacturing site's record review were followed up during the on-site PLI (see Compliance Management System (CMS) Work # 578783 and the records request memo dated May 10, 2024). An on-site PLI of the Biotest AG facility (Dreieich, Germany, FEI # 3001034985), which is used to manufacture the YIMMUGO (b) (4) DP and perform DP release testing, was conducted from December 4 – 15, 2023, by OCBQ/DMPQ and the Office of Therapeutic Products (OTP). A 10-item Form FDA 483 Inspectional Observations was issued at the conclusion of the Biotest AG PLI, and the PLI was classified as Voluntary Action Indicated (VAI).

In addition to the PLI and records review, facility inspections were waived following an evaluation of the inspection compliance histories of the DP release testing facilities:

(b) (4)

Note, the inspection waiver for these facilities is documented in a separate inspection waiver memo dated November 20, 2023.

Based on the information submitted to BLA 125810/0, PLI, and inspectional compliance history evaluations, the production process, facilities, equipment, and controls appear acceptable for the licensure of YIMMUGO, and approval is recommended.

## B. RECOMMENDATION

### I. APPROVAL

Based on the information provided in the original application and amendments, DMPQ recommends the approval of Immune Globulin Intravenous (Human) 10% liquid, YIMMUGO, which is manufactured at Biotest AG, Landsteinerstraße 5, 63303 Dreieich, Germany.

The approval includes a comparability protocol to increase the manufacturing capacity at the Biotest AG site by introducing a (b) (4)

(b) (4) The proposal to report the data from the comparability protocol in a changes being effected in 30 days (CBE-30) supplement appears acceptable.

The approval also includes the following inspectional recommendations for the Biotest AG facility located at Landsteinerstraße 5, 63303 Dreieich, Germany, (FEI 3001034985):

1. Regarding the (b) (4) vessels in Production Site (b) (4) Assess the (b) (4) (b) (4) evaluate the established practices to ensure the prevention of equipment contamination is still acceptable, and evaluate any deviations related to the contamination of the (b) (4) The (b) (4) validation study was not completed during the BLA review.
2. Regarding the product contact (b) (4) equipment in Production Site (b) (4) Assess the (b) (4) evaluate the practices to ensure the equipment remains free of contamination during the (b) (4) and assess any deviations associated with the contamination of the cleaned product contact (b) (4) equipment used during the (b) (4) of DP. The (b) (4) validation study was not completed during the BLA review.
3. Regarding the product contact (b) (4) equipment in Production Site (b) (4) Assess the (b) (4) evaluate the established practices to ensure the (b) (4) provides the equipment parts protection from contamination, and to evaluate any deviations associated with the contamination of the cleaned and sanitized product contact equipment used during the (b) (4) of DP to ensure that the (b) (4) was applied. Biotest changed the (b) (4) and the (b) (4) validation study was not completed during the BLA review.

CBER understands the inspectional recommendations may or may not be taken (based on risk and available resources) and is not requesting documentation to be submitted as evidence of completion.

**II. SIGNATURE BLOCK**

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Miriam Ngundi, CSO, OCBQ/DMPQ/MRB1	Concur	
Neetu Dahiya, Biological Reviewer, OCBQ/DMPQ/MRB1	Concur	
Lori Peters, Deputy Division Director/ Acting Branch Chief, OCBQ/DMPQ	Concur	
Carolyn Renshaw, Director, OCBQ/DMPQ	Concur	

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**3.2.S DRUG SUBSTANCE**

(b) (4)

A large rectangular area of the document is redacted with a solid grey fill, covering the majority of the page's content.

**3.2.S.2 Manufacture**

(b) (4)

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

(b) (4)

**3.2.S.2.3 Control of Materials**

**Source plasma**

The source plasma collected from healthy qualified plasma donors is obtained from FDA licensed plasmapheresis centers/establishments and complies with 21 CFR Part 640 Subpart G-source plasma.

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

### 3.2.P DRUG PRODUCT

#### 3.2.P.1 Description and Composition of the Drug Product

YIMMUGO drug product (DP) is a highly purified, sterile, non-pyrogenic, ready-to-use polyvalent human immunoglobulin solution. The DP, which is administered intravenously, is a 10% (100 mg/mL) solution consisting of ≥ 96% immunoglobulin G (IgG) active substance, (b) (4) glycine, (b) (4) polysorbate 80 stabilizers, and water for injection as solvent. YIMMUGO is presented as 50, 100, and 200 mL single doses filled in (b) (4) mL glass vials, respectively. The vials are closed with bromobutyl rubber stoppers (Type (b) (4) and flanged with flip-off aluminum caps. The solution is clear to slightly opalescent and colorless to pale yellow.

#### 3.2.P.2.5 Microbiological Attributes

No microbial preservative is added during the manufacture of YIMMUGO product. The microbial control during the manufacture of the DP includes sterile filtration and aseptic filling of final container vials. The DP release testing includes sterility per (b) (4) (b) (4) and bacterial endotoxins according to (b) (4). Sterility is assessed by the (b) (4) method with the acceptance criterion of sterile (no growth evident). The acceptance criterion for bacterial endotoxins is (b) (4). (b) (4) The routine production process includes container closure integrity testing (CCIT) using a validated (b) (4) with (b) (4) method. The container closure system (CCS), a combination of vial (b) (4) (b) (4) stopper, and seal was qualified using CCIT with a (b) (4) method. The testing was performed by (b) (4) located at (b) (4) (b) (4).

The CCIT (b) (4) method performed to qualify the CCS consisted of (b) (4) (b) (4)

The test results from all (b) (4) vial configurations met the acceptance criteria of no growth observed in the test vials. All positive controls and (b) (4) test vials showed (b) (4) while all negative control vials had no growth.

Biostat validated the CCIT (b) (4) method with (b) (4) based on (b) (4) (b) (4). The validation was performed (b) (4)

1 page has been determined to be not releasable: (b)(4)

In amendment STN125810/0.63, Biotest clarified that the CCIT procedure is performed at (b) (4) and (b) (4) is performed within (b) (4) (b) (4) when stored at (b) (4) per the method validation (b) (4). The applicant states that the routine manufacturing process includes testing of (b) (4) (b) (4) from each batch.

*Reviewer's comment:* The information provided appears acceptable. All results for the qualification of the CCS met the defined acceptance criteria, indicating that the CCS appears acceptable for YIMMUGO DP. The results of the validation of the CCIT (b) (4) (b) (4) method met the predefined acceptance criteria and appear to indicate that the method is suitable for its intended use.

### 3.2.P.3 Manufacture

#### 3.2.P.3.1 Manufacturer(s)

YIMMUGO DP is manufactured at Biotest AG, Landsteinerstrasse 5, Dreieich, Hesse, Germany, 63303.

*Reviewer's comment:* Biotest provided a final list of DP manufacturers in amendment STN 125810/0.38. See section 3.2.A.1 for the list of the manufacturing activities performed at the Biotest AG facility as well as a complete list of the other facilities used to manufacture (i.e., testing and storage) DP.

#### 3.2.P.3.3 Description of Manufacturing Process

To manufacture the DP, (b) (4) the final DP product and aseptically filled into final containers (b) (4) in a Grade (b) (4) environment with Grade (b) (4).

YIMMUGO (b) (4) Production Site (b) (4) Production Site (b) (4) the manufacturing building for the DP. YIMMUGO DP is manufactured according to STD-P-00221 and consists of the following (b) (4) unit operations, performed at (b) (4) with (b) (4) storage at 2 – 8 °C.

(b) (4)

1 page has been determined to be not releasable: (b)(4)

(b) (4)

Step <sup>(b) (4)</sup> Labeling and packaging of DP

The labeling and packaging processes are performed at (b) (4) and the labeled/packaged product is stored at 2 – 8 °C.

Reprocessing / reworking is not allowed during the manufacture of the DP. In amendment STN 125810/0.65, in response to information requested by OTP, Biotest acknowledged that reprocessing is not allowed as part of an original BLA and updated the relevant eCTD sections. The applicant stated that an update to STD-P-00221 will be performed within the established change control process after BLA approval to ensure regulatory compliance.

The batch sizes of the DP for each of the fill volume are as follows:

- 50 mL: (b) (4) vials
- 100 mL: (b) (4) vials
- 200 mL: (b) (4) vials

*Reviewer's comment: The sponsor provided a clear stepwise description of the DP manufacturing process. In amendments STNs 125810/0.63, 125810/0.75, and 125810/0.79, Biotest revised Section 3.2.P.3.3 including the flow chart demonstrating the overview of essential steps of the manufacturing process as well as the narrative. The revisions included addition of CCIT as an in-process test, removal of the use of (b) (4)*

*Biotest included the flow chart (with associated SOPs) of the DP manufacturing process in Section 3.2.R, Description of Manufacturing Process and Controls, Drug Product (Document STD-P-00221), Figure 2.*

### 3.2.P.3.4 Controls of Critical Steps and (b) (4)

The sterile filtration (b) (4) during the (b) (4) process (b) (4) is a (b) (4) to microbial quality in the manufacture of the DP. The step is controlled by (b) (4) testing performed after the aseptic filling process. Biotest stated that the (b) (4) test results support the sterility test performed on filled containers and covers a (b) (4) sample of the manufactured batch. The (b) (4) (b) (4) test is performed using the (b) (4) test with an acceptance criterion of a (b) (4). The results of the (b) (4) tests performed for the (b) (4) PPQ batches and (b) (4) validation batch with clinical material met the acceptance criteria (b) (4).

The critical process parameters (CPPs) assessed during the manufacture of the DP including storage temperatures, maximum storage periods, pH, and bioburden are provided in Section 3.2.P.3.3 above.

No (b) (4) is produced during the manufacture of YIMMUGO DP.

*Reviewer's comment: The information provided appears acceptable. The (b) (4) (b) (4) appears acceptable. The results of the process validation data appear to support the acceptance criteria for (b) (4) test. Furthermore, the process validation data provided in Section 3.2.P.3.5 appear to support the selection and justifications for the CPPs, ranges, and in-process controls. Overall, the data appear to indicate an appropriate control strategy is implemented to assure product quality and sterility and process consistency.*

### 3.2.P.3.5 Process Validation and/or Evaluation

In Table 3.2.P.3.5-1, Biotest provided the following list of process validation studies performed to support of the manufacture of YIMMUGO DP:

(b) (4)

(b) (4)

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

### 3.2.P.5 Control of Drug Product

#### 3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

In Table 3.2.P.5.1-1, Biotest provided the YIMMUGO DP specifications for release testing including the following acceptance criteria:

- Visual inspection: Clear and free from particles
- Sterility: Sterile (no growth observed)
- Bacterial endotoxins: (b) (4)

Biotest stated that the justification of the specifications is in accordance with (b) (4) (b) (4) methods. The applicant explained the YIMMUGO final product must be clear and free from particles according to (b) (4) on (b) (4). Biotest performs 100% visual inspections on all filled DP containers. The test is performed according to (b) (4). Sterility test is performed using (b) (4) method per (b) (4) for US batches. Bacterial endotoxins are tested using the (b) (4) method in accordance to (b) (4).

#### 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

The visual inspection method used for DP release to determine the absence of visible particles is conducted according to (b) (4). Biotest stated that there are no additional validation parameters assessed for visual inspection procedures based on (b) (4). In amendment STN 125810/0.67, Biotest clarified that following the 100% inspection of each batch, samples are (b) (4) for a subsequent visual inspection by Quality Control using the acceptable (b) (4) test. The applicant explained the visual inspection for the (b) (4) is performed using the (b) (4) for the 100 % visual inspection.

Biotest used (b) (4)

In amendment 125810/0.67, Biotest provided the number of samples for the different lot sizes (Table 8), the (b) (4) according to the lot size and defect class (Table 9), and the definition and location/pattern of critical, major, minor, and cosmetic (b) (4) defects (Tables 10 and 11). All the containers with critical, major, minor, and cosmetic (b) (4) defects are sorted out during the visual inspection. The applicant also provided the (b) (4) acceptance criteria for each defect type based on the number of samples (batch size).

The CCIT using the (b) (4) method with (b) (4) is performed as an in-process control and for stability testing (validation of the method is documented under 3.2.P.2.5 Microbiological Attributes)

*Reviewer's comment: The information provided appears acceptable. Visual inspection and sterility methods are performed in accordance to (b) (4) methods. Biotest validated the CCIT method (provided in Section 3.2.P.2.5 Microbiological Attributes), and the results met the predefined acceptance criteria. The endotoxin and sterility method validations are deferred to DBSQC and all other release tests are deferred to OTP.*

### 3.2.P.5.4 Batch Analyses

Biotest provided the batch analyses for (b) (4) batches of the YIMMUGO DP manufactured during the process validation using (b) (4) batches of (b) (4) manufactured in Production Site (b) (4). The filling sizes of the DP batches were (b) (4). The results for all the lots met the acceptance criteria for visual inspection (clear and free from particles), sterility (sterile), and pyrogen (pyrogen free; (b) (4) (b) (4)). Biotest stated that the (b) (4) test was replaced by bacterial endotoxin test (b) (4) in the release specification.

*Reviewer's comment: The information provided appears acceptable. All tests results for visual inspection, sterility, and bacterial endotoxin met the release acceptance criteria for all lots. The data appear to indicate that a sterile YIMMUGO DP can be consistently manufactured at Biotest AG.*

### 3.2.P.7 Container Closure System

The primary container closure system (CSS) for YIMMUGO DP consists of the components:

- Glass vials – (b) (4) (product contact): Clear, colorless type (b) (4) (b) (4). All the vial sizes have a flange diameter of 32 mm. The vials are supplied by (b) (4) or equivalent manufacturer with comparable quality. The vials are washed and sterilized/depyrogenated at the DP filling area prior to filling.
- Stopper (product contact): 32 mm bromobutyl type (b) (4) rubber stoppers. The stoppers are supplied siliconized and pre-cleaned by (b) (4) or equivalent manufacturer with comparable quality. The stoppers are sterilized at the DP (b) (4) areas prior to use.
- Seal: 32 mm aluminum flip-off seal, supplied by (b) (4) (b) (4)

Biotest provided the dimensions all components of the CCS (vials (all sizes), stopper, and seal) as well as the samples of the certificates of analysis from the different manufacturers.

Regarding the vials and stoppers supplied by an “equivalent manufacturer with comparable quality,” in amendment STN 125810/0.80, Biotest confirmed new or additional suppliers of vials or stoppers will be reported in post-approval supplements.

*Reviewer's comment: The information provided on the primary container closure system for YIMMUGO DP appears acceptable.*

### 3.2.P.8 Stability

#### 3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

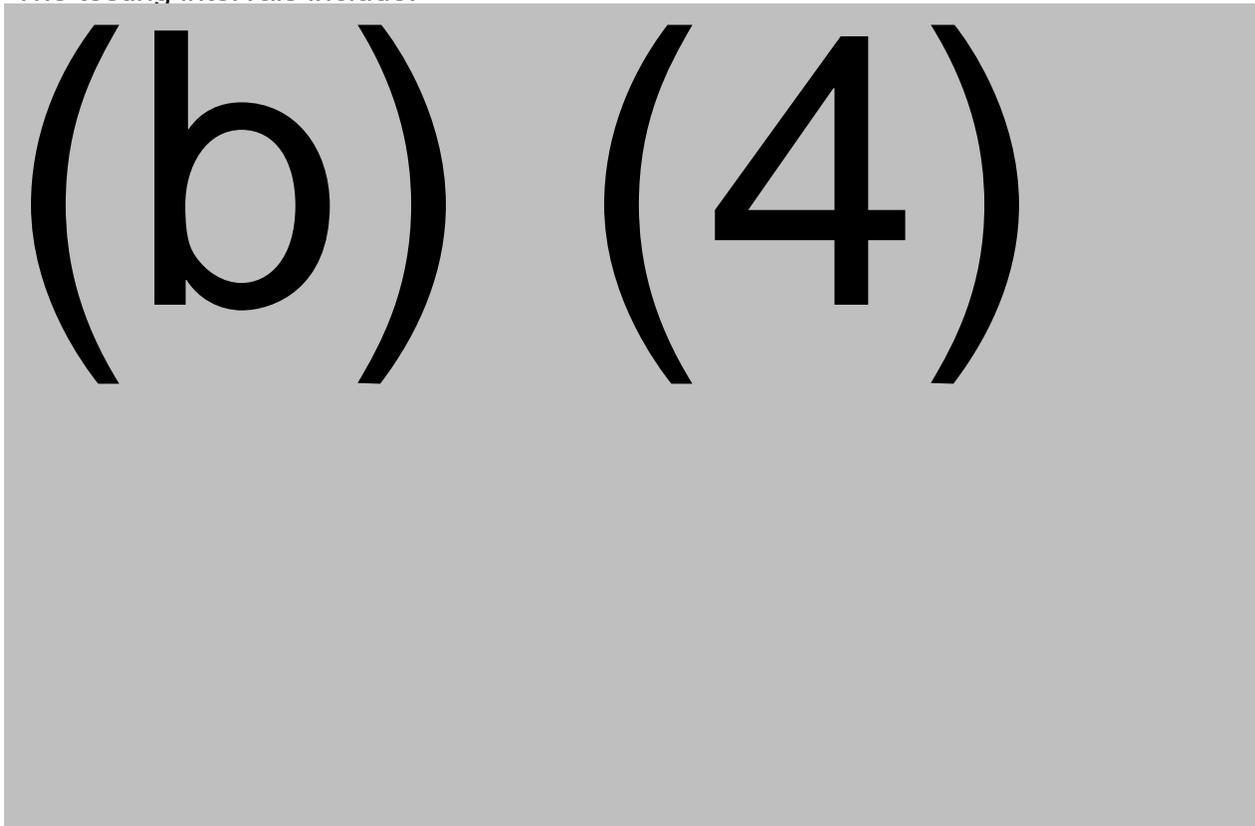
Biotest proposes a YIMMUGO DP shelf life of 30 months at  $5 \pm 3$  °C, which may include a one-off period of up to 6 months at room temperature (not above 25°C) (i.e., 24 months at 2 – 8 °C, then 6 months at (b) (4)

Samples for ongoing stability study BE-Q-301j-95 with (b) (4) PPQ batches filled in all three vial configurations (50, 100, and 200 mL) were stored as follows:



The available data are up to either 15 or 24 months.

The testing intervals include:



In amendment STN 125810/0.80, Biotest clarified that shelf life of 30 months includes the storage at both  $5 \pm 3$  °C and 25 (b) (4) conditions. The applicant provided Table 3.2.P.8.2-3 which listed the testing intervals for stability samples stored at 25 °C (b) (4) (b) (4) after 24 months storage at 5 °C (+/- 3 °C) within stability study 301j-95.

The test results to date from the stability study met the indicated acceptance criteria:

- Sterility (b) (4) Sterile

- Bacterial endotoxin (b) (4) (alert limit)
- Pyrogen (b) (4) pyrogen free
- CCIT – (b) (4) test (b) (4) (b) (4)

Biotest stated that the pyrogen test (b) (4) bacterial endotoxin test (b) (4) (b) (4) for lot release; however, both parameters are tested in the stability studies. Biotest explained the endotoxin test had not been implemented at the beginning of the stability study and in order to keep the data comparable at different time points, the pyrogen test will be continued until the approval of YIMMUGO DP or the end of stability studies.

In amendment STN 125810/0.51, Biotest provided the final stability protocol to be used for all future drug product lots.

In amendment STN 125810/0.67, Biotest clarified that CCIT (b) (4) with (b) (4) is used for the stability program for YIMMUGO DP in addition to sterility testing with (b) (4) product filled vial tested for CCI at each stability test point.

*Reviewer's comment: DMPQ defers the review of the stability testing protocols to OTP. The test results to date for sterility, endotoxin, pyrogen, and CCIT met the predefined acceptance criteria. The information provided appears acceptable.*

### 3.2.A APPENDICES

#### 3.2.A.1 Facilities and Equipment

##### Facilities Table

Facility: Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Comments/ Inspection history
Biotest AG Landsteinerstraße 5, 63303 Dreieich Germany FEI: 3001034985  • (b) (4) manufacture • (b) (4) release testing • DP manufacture • DP release testing • DP labeling and packaging • DP batch release	Inspection	Yes	Yes	OCBQ/DMPQ  VAI  December 4 – 15, 2023
(b) (4)       • DP release testing: Potency test for diphtheria toxin neutralization	Waiver	Yes	Yes	ORA/OPQO  PAI  (b) (4)  VAI

Facility: Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Comments/ Inspection history
(b) (4)  • DP release testing: Potency test for measles virus neutralization and polio virus neutralization	Waiver	Yes	Yes	ORA/OPQO Surveillance inspection (b) (4) NAI
(b) (4)  • DP release testing: Potency test for measles virus neutralization and polio virus neutralization	Waiver	Yes	Yes	ORA/OPQO Surveillance inspection (b) (4) NAI
(b) (4)  • DP release testing: Potency test for diphtheria toxin neutralization, measles virus neutralization, and polio virus neutralization	Waiver	Yes	Yes	ORA/OBPO surveillance inspection (b) (4) VAI
(b) (4)  • DP storage	Not required	No	Yes	No inspection history
(b) (4)  (b) (4)  • DP storage	Not required	No	Yes	OCBQ/DMPQ PAI (b) (4)  VAI

\*The alternative testing sites may be used when e.g., the primary laboratory is not able to test samples or as a secondary site for stability samples.

Acronym key: DMPQ - Division of Manufacturing and Product Quality; DP – drug product; (b) (4) (b) (4) NAI – No Action Indicated; OBPO – Office of Biological Products Operations; OCBQ - Office of Compliance and Biologics Quality; OPQO – Office of Pharmaceutical Quality Operations; ORA – Office

of Regulatory Affairs; NAI – No Action Indicated; PAI – Pre-approval inspection; PLI – Pre-license inspection; VAI – Voluntary Action Indicated

**Facility Design**

Biotest AG at Landsteinerstraße 5, 63303 Dreieich, Germany, which manufactures YIMMUGO, is a multiproduct facility that develops and produces immunoglobulins, coagulation factors and albumin products based on human plasma. The manufacture of YIMMUGO (b) (4) DP and drug product release testing is performed at this facility.

The facility consists of following (b) (4) main production sites:

(b) (4)

(b) (4)

(b) (4)

*Reviewer's comment:* The cleanroom classification appears acceptable for the activity performed. The information provided appears acceptable.

**Drug product – Production Site** (b) (4)

YIMMUGO DP is manufactured at Production Site (b) (4) which consists of Buildings (b) (4) (b) (4). The manufacturing building also referenced as Building (b) (4) is a multi-product facility, and all products manufactured in the building originate from human plasma. Building (b) (4) consists of (b) (4) (levels) where the following activities are performed:

(b) (4)

In amendment STN 1125810/0.21, Table 4, Biotest provided the rooms used to manufacture YIMMUGO DP. The critical rooms and activities performed include:

(b) (4)

- Visual inspection (b) (4)
- Labeling and packaging (b) (4)

In Table 3.2.A.1.3-3 and amendment STN 125810/0.21, Table 4, Biotest provided a list of the rooms (support areas) that are used for the manufacture of YIMMUGO. These areas include:

(b) (4)

*Reviewer's comment:* The information provided appears acceptable. The cleanroom classifications appear acceptable for their respective manufacturing operations.

#### Flow Diagrams

In amendment STN 125810/0.21, Biotest stated that there is no product-specific flow diagrams within the production facility, and floor plans were generated in response to an IR. The diagrams showed that the flow in the manufacturing areas is (b) (4). Formulated DP is (b) (4). Materials to the (b) (4). (b) (4)

(b) (4)

(b) (4)

**Drug product – Production Site** (b) (4)

Personnel: Personnel entry and exit to Production Site (b) (4) is according to established procedures, which provide the requirements for access control and gowning. The applicant provided the narratives for personnel entry/exit to the manufacturing areas.

Materials: Materials (e.g., vials, stoppers, boxes) are delivered to a dedicated entry point (delivery area) in Building (b) (4) and transported to the production area via a dedicated material (b) (4). Material from the delivery area to the (b) (4) is transported to via (b) (4) and (b) (4).

Waste: (b) (4)

Product: (b) (4)

Equipment: Biotest stated that there are no floor plans for cleaned and uncleaned equipment within the Production Site (b) (4). Biotest explained that the equipment is handled according to an established procedure. Biotest explained that the support areas have a defined equipment flow and specific requirements, which ensures that the paths of cleaned and soiled equipment do not cross. The areas are marked with a floor marking for segregating clean and dirty equipment. Additionally, cleaned equipment is labeled.

In amendment STN 125810/0.21, Biotest provided the floor diagrams indicating the air handling unit(s), air pressure differentials, air flow, and room classifications for the manufacturing area. The main manufacturing areas (b) (4)

The inspection rooms and labeling/packaging areas in Building (b) (4) are served by (b) (4). The (b) (4) serves to (b) (4). The manufacturing rooms have a pressure cascade where rooms with a higher classification have higher pressure than the lower classified rooms as follows:

(b) (4)

Air flow direction is from area of higher classification to lower classified areas.

*Reviewer's comment: While the narrative for the diagram flows was limited, the drawn-in flows appear to indicate an orderly movement of personnel as well as transfer of materials, product, and waste. Personnel entry and exit to the filling room use the same (b) (4). There is only (b) (4) individual at a time allowed through the (b) (4). Personnel movement through those (b) (4) is in sequence from a Grade (b) (4) to Grade (b) (4) then to Grade (b) (4) before entering the filling area (Grade (b) (4)). Different gowning levels are required through the (b) (4). There is temporal segregation of product and waste during transfer through the shared areas. The temporal segregation through the (b) (4) appears acceptable. Flows for personnel,*

materials, product, and waste were evaluated during the PLI. SOP-P-00360, which describes the operations at the support areas, provides the details with drawings showing the demarcated areas for the clean and dirty equipment. The information provided appears acceptable.

**Contamination and cross-contamination controls**

In Table 3.2.A.1.1-4, Biotest provided a list of the (b) (4) products manufactured in the facility. None of the products (human plasma derived products) are approved for the US market. To minimize the contamination/cross-contamination risk from multiple products and different batches of YIMMUGO, Biotest implemented the following general controls:

(b) (4)

(b) (4)

**Drug product – Production Site** (b) (4)

(b) (4)

amendment STN 12581/0.21, Biotest described the controls used to prevent contamination and cross-contamination. The applicant explained that after each production run, the used equipment is cleaned and (b) (4)-sanitized or sterilized according to established procedures. To avoid mixing of dirty and cleaned equipment, there are specific storage and handling areas defined according to established

procedure. Additionally, a preparation control card is attached to each equipment or equipment set. The card documents the status of the equipment (e.g., previous use (batch number), cleaning date, holding times, sterilization date, planned use (batch number)). After the manufacture of each batch, production areas are cleaned and disinfected according to established procedures. Line clearance is performed after and before each filling process according to established procedures. A cleaning check is performed before the start of the filling line set-up and documented in the batch record.

*Reviewer's comment: The controls in place, which include facility design, differential pressure control, flows, specific gowning requirements and other measures listed above to mitigate contamination and cross-contamination risks, appear acceptable and were evaluated during PLI. The use of shared product-contact equipment appears acceptable as the (b) (4) viral clearance steps performed during the manufacture of the (b) (4) appears acceptable to mitigate the risk of (b) (4) contamination from products manufactured using non-US source plasma.*

### **Facility cleaning and disinfectant effectiveness studies**

In amendment STN 125810/0.21, Biotest provided a narrative of the two disinfectant effectiveness studies performed and stated that another study was ongoing with a report scheduled for November 2023. In amendment STN 125810/0.63, Biotest clarified that the referenced ongoing (now completed) study VAL-H-00032 V.1.0 was a cleaning process validation to demonstrate the efficacy of the cleaning and disinfection process in combination with the cleaning agents, materials, and disinfectants used. This study did not include disinfectant efficacy tests according to (b) (4)

In amendment STN 125810/0.63, Biotest provided the summary reports of the three disinfectant effectiveness validation studies performed according to (b) (4) each study had different objectives. Study VAL-H-00002\_REP-01 V.1.0 tested a variety of possible bactericidal and sporicidal chemical disinfectants. Study VAL-H-00017\_REP-01 V.1.0 focused on the efficacy of sporicidal agents against (b) (4) (b) (4) due to the accumulated recovery of the bacterial (b) (4) (b) (4) during the EM qualification of classified rooms in Production Site (b) (4) in 2019. Biotest determined that the most likely the root cause for the incidences was inadequate cleaning. Therefore, a corrective action included an additional disinfection study. Study VAL-H-00065\_REP-01 V.1.0 assessed the efficacy of sporicidal agent (b) (4) against (b) (4) All three studies assessed various contact times and different surfaces including (b) (4)

The summary for each study is as follows:

#### *Study VAL-H-00002\_REP-01 V.1.0*

- Disinfectants tested: (b) (4)

- Organisms challenged: (b) (4)

All the results for the tested contact times met the acceptance criteria of (b) (4) reduction for bacteria and yeast as well as (b) (4) reduction for spores and mold, except for one disinfectant. (b) (4) at (b) (4) contact time did not meet the acceptance criteria of (b) (4) reduction for (b) (4).

*Study VAL-H-00017\_REP-01 V.1.0*

- Disinfectants tested: (b) (4)

- Organisms challenged: (b) (4)

All the results for the tested contact times met the acceptance criteria of (b) (4) reduction for the spores, except for one disinfectant. Test results for (b) (4) (b) (4) at (b) (4) contact time did not meet the acceptance criteria of (b) (4) reduction for (b) (4)

*Study VAL-H-00065\_REP-01 V.1.0*

- Disinfectants tested: (b) (4)

- Organisms challenged: (b) (4)

All the results for the tested contact times met the acceptance criteria of (b) (4) reduction for bacteria and yeast as well as (b) (4) reduction for spores and mold, except for one disinfectant. (b) (4) at (b) (4) contact time did not meet the acceptance criteria of (b) (4) reduction for (b) (4)

In amendment STN 125810/0.63, Biotest provided the disinfectants (bactericidal and sporicidal) and frequency of use during routine facility disinfection. In Grades (b) (4) and (b) (4) areas (Production sites (b) (4) are used as disinfectants (b) (4) are used as sporicidal agents. In Grade (b) (4) areas (found only in Production site (b) (4) are used as disinfectants while (b) (4) (b) (4) and (b) (4) are used as sporicidal agents.

Biotest states that the SOPs defining the disinfectants that are routinely used (SOP-H-00136 "On-site Cleaning and Disinfecting Agents" and SOP-H-00023 "Cleaning and disinfection of cleanrooms grade (b) (4) and (b) (4) are currently being revised to reflect the results of the disinfectant efficacy study VAL-H-00065\_REP-01 V.1.0. As a result of the changes, the information provided in amendment STN 125810/0.63 indicate that (b) (4) will not be used as sporicidal agents.

*Reviewer's comment: The information provided appears acceptable. Based on the revised SOPs for facility disinfection, it appears that the disinfectants used in the facility met the efficacy acceptance criteria according to consensus standards. The frequency of cleaning and disinfection performed on (b) (4) in Production Sites (b) (4) appears acceptable.*

### **Utilities**

The utilities at Biotest includes the heating, ventilation, and air conditioning (HVAC) system, water system (water for injection and purified water), pure steam, and gas systems. The critical utility systems have been qualified, are routinely monitored, and undergo preventive maintenance (PM) in accordance with SOPs.

### **HVAC: Qualification, EMPQ, and routine monitoring**

(b) (4)

1 page has been determined to be not releasable: (b)(4)

(b) (4)

All EMPQ deviations were investigated, corrective actions were implemented, and all critical/non-critical deviations were closed.

EM is performed (b) (4) for Grade (b) (4) areas and (b) (4) for Grade (b) (4) areas and the criteria are the same as EMPQ, which is in accordance with (b) (4). Routine EM data was provided in amendment 125810/0.20. Biotest submitted annual EM reports for 2021 and 2022. A total of (b) (4) tests were performed in year 2022 and there was (b) (4) warning value exceedances and (b) (4) action value exceedances.

*Reviewer's comment: The results of EMPQ met the acceptance criteria and appear acceptable to demonstrate that the environment in the manufacturing areas is under control. The sampling locations are uniformly distributed in accordance with the (b) (4) standard. The routine EM limits appear acceptable based on the (b) (4) (b) (4). All critical and non-critical deviations were investigated with corrective actions implemented. The information provided appears acceptable.*

**Drug product – Production Site (b) (4)**

In amendment STN 125810/0.21, Biotest provided the HVAC system for Production Site (b) (4). The system consists of (b) (4) AHUs (subsystems) as follows:

(b) (4)

(b) (4)

In amendment STN 125810/0.63, Table 10, Biotest provided the specific air exchange rate for each of the manufacturing rooms and associated airlocks in Production Site (b) (4). Air exchange rates at (b) (4) rooms (Grade (b) (4)) and filling suites (Grade (b) (4)) are (b) (4) and (b) (4) respectively.

All AHUs use (b) (4) except for (b) (4) which uses (b) (4). The pressure differentials are continuously monitored using the Building Monitoring System (BMS) with alarms triggered when the differentials fall outside the alarm set points.

In amendment STN 125810/0.28, Biotest provided a summary of the qualification of the HVAC and the environmental monitoring performance qualification (EMPQ) performed over a (b) (4) period (b) (4). The OQ measurements were performed over several days for each AHU ranging between (b) (4). In amendment STN 125810/0.63, Biotest stated that the critical parameters assessed during the OQ included (b) (4) and met the predefined acceptance criteria. Biotest explained that the integrity of all (b) (4) is tested (b) (4) for Grade (b) (4) and (b) (4) rooms and (b) (4) for Grade (b) (4) areas according to (b) (4) requirements. (b) (4) rates are verified (b) (4) with acceptance criteria ((b) (4) of (b) (4) (Grade (b) (4) and (b) (4) (Grades (b) (4) and (b) (4)). Online monitoring of (b) (4) is performed in Grade (b) (4) areas and verified (b) (4) by (b) (4). (b) (4) are continuously monitored online.

The EMPQ was performed under (b) (4) conditions with measurements performed over (b) (4) days ranging between (b) (4) and (b) (4), and acceptance criteria (Tables 8 and 9) were according to (b) (4). Biotest stated that the (b) (4) measurements were performed during the (b) (4) different work shifts (b) (4). The EMPQ results for (b) (4) and (b) (4) met the acceptance criteria based the (b) (4) requirements for the different room classifications (Grades (b) (4)) after deviations were resolved.

In amendment STN 125810/0.63, Biotest provided the species of bacteria identified in the major eight deviations that occurred in Grades (b) (4) and (b) (4) areas. The identified microbials were (b) (4) (not further identified). Biotest explained that the identified microbials are found in the environment, air, soil, and human skin. Biotest clarified that

as part of addressing the deviations, the specified EMPQ monitoring locations in the (b) (4) rooms were relocated to the identified critical areas after the initial measurement for the remainder of the EMPQ and for routine EM.

In amendment STN 125810/0.67, attachments 4.1 and 4.2, Biotest provide the details of the deviations that occurred during EMPQ including the deviation number and category; date, area, activities being performed, operating conditions; test and failing results against the acceptance criterion; species of viable microbes identified, if applicable; and the summary of root cause investigation and CAPA, if applicable. Biotest clarified that the qualification was performed during the routine operation of Production Site (b) (4) over a (b) (4) period and some of the documented deviations occurred in areas not used to manufacture YIMMUGO DP. The deviations registered during the 2015 EMPQ were due to (b) (4) (not identified) not meeting the acceptance criteria. There were only three deviations within the (b) (4) suite during the 2015 EMPQ including (b) (4) area (Grade (b) (4) (b) (4) area (Grade (b) (4), and (b) (4) at the (b) (4) area (Grade (b) (4). All deviations registered during the 2016 EMPQ were due to (b) (4) with no deviation in the DP (b) (4) suite. The microbials recovered during the 2016 EMPQ were identified to be present in environment, air, soil, and human skin. Biotest explained that all deviations were resolved by repeat measurements at all the affected areas, and the results of the repeat measurements met the required acceptance criteria.

In amendment STN 125810/0.63, Biotest stated that routine EM is performed as follows:

(b) (4)

In amendment STN 125810/0.63, Tables 24 – 28, Biotest provided the alert and action limits for (b) (4) for the classified areas during routine EM. The action limits correspond to the acceptance criteria used for the EMPQ. Biotest explained that for each out-of-limit (OOL) result exceeding the alert limits a deviation is opened, and an investigation was performed. Additionally, the release of a batch can only occur after completion of all OOL investigations. Results exceeding alert and action limits are trended. Biotest explained that a monitoring location identified as a hot spot would result in a deviation and further investigation. A hot spot is defined as a location with three action limit exceedances or (b) (4) consecutive action limit exceedances within the last (b) (4) measurements, and (b) (4) consecutive alert limit exceedances are treated as (b) (4) action limit exceedance.

In Table 3.2.A.1.3-2, Biotest provided the (b) (4) limits applied to each of the room classifications and explained that controlled non classified (CNC) areas have restricted access through card key access, gowning requirements, and a temperature control system. In amendment STN 125810/0.63, Biotest stated that CNC areas do not have to

meet any classification requirements for particle concentrations, microbiological, temperature, or relative humidity.

*Reviewer's comments: The information provided for Production Site 3 appears acceptable. The acceptance criteria for the EMPQ and the limits for routine EM are in accordance with industry standards and regulatory guidance (i.e., FDA Aseptic Processing Guidance, (b) (4) [redacted]. The EMPQ was performed during routine product manufacturing, including during the manufacture of other products besides YIMMUGO, which may explain the long list of deviations provided. Few deviations were associated with the aseptic filling areas, and all deviations appear to have been resolved.*

**Water systems**

There are separate water systems (water for injection, purified water, and pure steam) for Production Site <sup>(b) (4)</sup> [redacted] and Production Site <sup>(b) (4)</sup> [redacted].

(b) (4)

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

(b) (4)

**Drug product – Production Site** (b) (4)

*Water for injection (WFI)*

The WFI in Production Site (b) (4) is used during DP (b) (4)

In amendment STN 125810/0.21 and STN 125810/0.63, Biotest stated that the WFI is monitored (b) (4)

In amendment 125810/0.63, Biotest clarified that the limits applied during routine monitoring are the acceptance criteria assessed during PQ.

*Purified Water (referred to as Aqua Purificata (AP))*

The AP in (b) (4)

Biotest provided a description of AP generation as well as a schematic diagram of AP generation, storage, sample points, and points of use. (b) (4)

In amendment STN 125810/0.28, Biotest provided the summary qualification report for AP (QAL-06102023-001). (b) (4)

The qualification test results met the acceptance criteria (QAL-06102023-001, Tables 10 and 11). Biotest stated that there no critical deviations that occurred during the qualification of AP. The applicant stated that the periodic maintenance of AP generation and distribution system is performed according to an established schedule.

In amendment STN 125810/0.21, Biotest stated that the AP at (b) (4)

*Pure Steam (PS)*

Pure steam is used for the (b) (4)

Biotest provided a schematic diagram and description of the generation and distribution of the PS.

In amendment STN 125810/0.28, Biotest provided the summary qualification report for pure steam (QAL-08102023-001). (b) (4)

The qualification test results met the acceptance criteria after deviations were resolved (QAL-08102023-001, Tables 10 – 12). Biotest stated that periodic maintenance of PS generation and associated system parts is performed according to an established schedule.

In amendment STN 125810/0.21, Biotest stated that the pure steam at the production and distribution systems are monitored (b) (4)

In amendment STN 125810/0.63, Biotest clarified that routine monitoring is performed at limits corresponding to the acceptance criteria assessed during PQ.

*Reviewer's comment: The information provided for water system appears acceptable. The results for the PQ met the predefined acceptance criteria, which are in accordance*

with industry standards (b) (4) and the same criteria are applied for routine monitoring. The investigations into the deviations and the resolutions appear acceptable. Biotest's conclusion that the deviations had no impact on the qualification of the water systems of Production Site (b) (4) appears acceptable.

**Gas systems**

(b) (4)

**Drug product – Production Site (b) (4)**

Compressed air (CA)

Compressed gas is used to (b) (4)

In amendment STN 125810/0.63, Biotest provided the summary qualification report for the CA including the certificates for the completion of the IQ and OQ. Biotest performed (b) (4) PQ runs over a (b) (4) and (b) (4). During the PQ, the measurements were taken (b) (4) and/or (b) (4). Biotest stated that the PQ test met the acceptance criteria for (b) (4) (Grade (b) (4) according to (b) (4)).

(b) (4) as well as for (b) (4) (Class (b) (4) per (b) (4) after deviations were resolved (Table 11).

In amendment STN 125810/0.21, Biotest stated that CA is tested (b) (4) In amendment 125810/0.63, Biotest clarified that the limits applied during routine monitoring are the acceptance criteria assessed during PQ.

(b) (4)  
(b) (4)

(b) (4)

(b) (4)

(b) (4)

*Reviewer's comment:* The information provided for gas system appears acceptable. The results for the PQ met the predefined acceptance criteria, which are in accordance with industry standards (i.e., (b) (4) and the same criteria are applied for routine monitoring. The investigations into the deviations and the resolutions appear acceptable. Biotest's conclusion that the deviations had no impact on the qualification of the (b) (4) (b) (4) Production Site (b) (4) appears acceptable.

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

(b) (4)

The (b) (4) studies, which are deferred to the CMC reviewers, appear to demonstrate that the (b) (4) treatment manufacturing step is effective against (b) (4) vation along with (b) (4) conditions (b) (4) (b) (4), as equipment is shared for the manufacture of products using US (b) (4) source plasma. In 2003, FDA held a Transmissible Spongiform Encephalopathies Advisory Committee meeting to discuss the methods used in plasma derivative manufacturing, including the common and routinely used cleaning methods for equipment that include the use of (b) (4). The committee acknowledged that blood was a low-risk tissue and that the current processing of plasma was likely to greatly reduce the risk of infectivity in most derivative products. There was consensus that the processes for cleaning of equipment that many manufactures are currently performing is adequate, but cleaning procedures should be standardized and effective methods adopted by all manufacturers. During this 2003 Advisory Committee meeting, Biotest's use of (b) (4) was presented. At the conclusion of the Advisory Committee meeting, it was agreed that when new scientific information relevant to plasma processing equipment becomes available it should be reviewed, and current cleaning techniques should be reevaluated. From 2003 to 2015 (FDA terminated the Advisory Committee in 2016 due to a declining number of issues that required the committee's advice), the cleaning methods in plasma derivative manufacturing facilities have not been discussed during the Advisory Committee meetings.

In FDA's May 2022 guidance, "Recommendations to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Components," the agency has revised its recommendation on reducing the possible risk of transmission of vCJD by blood and blood components. In the FDA's guidance of the same title dated April 2020 and

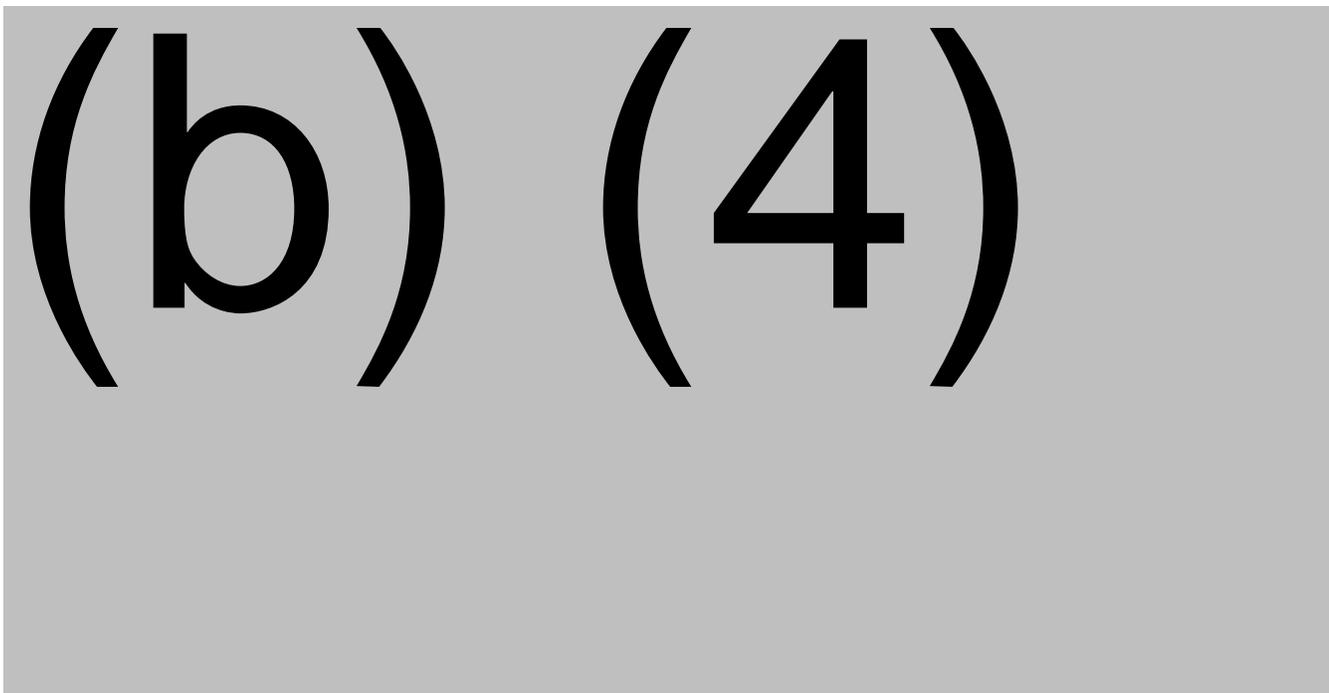
*updated August 2020, the agency had revised its recommendation on reducing the possible risk of transmission of CJD and vCJD by blood and blood components; these recommendations made in the 2020 guidance remained unchanged for the May 2022 guidance. Under these revisions, donors previously deferred for specific reasons (e.g., geographic risk) can be assessed for requalification and may be eligible to donate. Therefore, based on FDA's risk-ranking model and evaluation of new data and mathematical models to assess the relevance of donor deferral for geographical risk to blood safety, it appears FDA considers there to be no to minimal additional relative risk of exposure to CJD and vCJD from specific donors (e.g., specific geographical non-US blood and blood components).*

*The information provided appears acceptable.*

**Cleaning of (b) (4)**

**(b) (4)**

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



**Drug product – Production Site** <sup>(b) (4)</sup>

Biotest stated that all key process equipment used in Production Site 3 to manufacture YIMMUGO DP is also used for the production of established plasma based commercial products for non-US markets. Therefore, there is no dedicated equipment.

In Tables 3.2.A.1.3-15 and 3.2.A.1.3-16, Biotest provided the list of key process equipment used to manufacture YIMMUGO DP. The equipment list included the process step (b) (4) <sup>(b) (4)</sup> equipment number (ID), use of equipment, material of construction for product-contact pieces, cleaning method, sanitization/ sterilization method, and location (room number and classification). The critical process equipment used to manufacture YIMMUGO DP include:

Equipment	Product-contact / Use	Room / Classification	Cleaning	Sanitation / Sterilization
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15 pages have been determined to be not releasable: (b)(4)

(b) (4)

*Reviewer's comment: The information provided appears acceptable.*

**Drug product – Production Site** (b) (4)

The following (b) (4) rooms in Production Site (b) (4) and the warehouse are used to store the temperature sensitive product/materials at (b) (4)

(b) (4)

(b) (4)

*Reviewer's comment:* The information provided appears acceptable. The results of the PQ of the (b) (4) storage rooms met the predefined acceptance criteria, which appear to demonstrate the required temperatures are maintained in the (b) (4) rooms.

**Computer systems**

The major computer systems that support the manufacture of YIMMUGO include:

(b) (4)

(b) (4)

Biotest explained that the computer systems are qualified by approved procedures, which include design reviews and verification testing (IQ/OQ) and PQ is performed after the implementation of the software.

*Reviewer's comment: Qualification of the major computer systems were reviewed during the PLI.*

### 3.2.R Regional Information (USA) Comparability Protocols

(b) (4)

As provided in the original BLA and amendment 125810/0.75, Biotest is (b) (4) increase the manufacturing capacity. Biotest is planning to (b) (4)

using (b) (4) Currently, Biotest is

The proposed validation includes the following:

(b) (4)

Biotest stated that there are no changes to the process and associated parameters for the (b) (4) PPQ studies will evaluate the following microbial parameters:

(b) (4)

(b) (4)

(b) (4)

*Reviewer's comment: Biotest's plan to (b) (4) and the proposed qualification and cleaning validation plan appear acceptable. There appears to be no changes to the process parameters and acceptance criteria to process the (b) (4). The proposed reporting category of a CBE-30 appears acceptable. The information provided appears acceptable.*