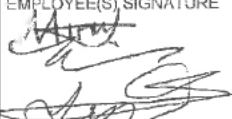


Biotest AG

Dreieich, Germany

FEI: 3001034985

December 4 - 15, 2023

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
DISTRICT OFFICE ADDRESS AND PHONE NUMBER CBER/OCBQ/Division of Manufacturing and Product Quality 10903 New Hampshire Avenue, Silver Spring, MD 20993 Lead Insp.: Miriam Ngundi Telephone: 240-402-9774 Industry Information: www.fda.gov/oc/industry		DATE(S) OF INSPECTION December 4-8 and 11-15, 2023	
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED TO: Peter Janssen, COO, Head of Industrial and Commercial Operations		FEI NUMBER 3001034985	
FIRM NAME Biotest AG	STREET ADDRESS Landsteinerstrasse 5		
CITY, STATE AND ZIP CODE 63303 Dreieich, Germany	TYPE OF ESTABLISHMENT INSPECTED Drug substance and drug product manufacturer		
THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS; AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.			
DURING AN INSPECTION OF YOUR FIRM, (I/WE) OBSERVED:			
<p>1. Inadequate quality oversight to assure that the Yimmugo drug product has the identity, strength, quality, and purity it purports or is represented to possess. For example:</p> <p>a. There is no quality oversight of unplanned maintenance events to assess the qualification/validation status and product impact. Specifically:</p> <p>i. SOP-T-00386 v. 5.0 "Maintenance of technical systems" does not require the quality unit's approval for any unplanned maintenance or repairs to the facility.</p> <p>ii. Work order 5031880, which was opened to repair a door to formulation room (b) (4) where the open final formulation operation for Yimmugo is performed, was not approved by the quality unit. A product impact assessment was not performed to assess the room's environment status while the door was not properly closed.</p> <p>b. Written procedures for production and process control are inadequate. For example:</p> <p>i. SOP-Q-00431 v. 5.0 "Review and release of plasma deliveries" does not contain the process on how to inspect plasma (b) (4)</p> <p>ii. (b) (4) -00488 v. 4.0 "Aseptic final (b) (4) of IgG Next Generation (BT595) and (b) (4) (b) (4) on the (b) (4) line," which is used for (b) (4) does not require the removal of documents including batch records. Line clearance was not performed in capping and crimping room (b) (4) where batch records for (b) (4) were found during the manufacture of Yimmugo batch (b) (4) on December 06, 2023.</p> <p>c. Written procedures are not followed. For example, (b) (4) (b) (4) should be prepared in accordance with (b) (4) -00185 v.2.0 "Preparation of (b) (4) (b) (4) However, on December 6, 2023, an analyst was observed (b) (4) containing approximately (b) (4) (b) (4)</p> <p>d. Written procedures are inadequate or not established. For example, the training program provided in (b) (4) -00007 v. 3.0 "Training Management" states that a risk assessment is to be performed to (b) (4)</p>			
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<p>(b) (4) However, (b) (4) -00007 does not include instruction on how to perform the risk assessment, including what criteria to evaluate, nor is there another established procedure to provide instruction on how to perform the risk assessment.</p> <p>e. Documentation practices are insufficient. For example, the number of test samples used to verify the functionality of the control systems along the labeling and packaging line (b) (4) was not documented on form (b) (4) -00187 at the time of performance during the labeling and packaging of Yimmugo 10%, 100 mL, lot (b) (4) on December 7, 2023.</p> <p>f. Preventive maintenance of critical equipment is not established. For example, there is no preventive maintenance for the following: pH meter (b) (4) used to measure the pH during final formulation; pH meter (b) (4) used in step (b) (4) anion exchange chromatography; and pH meter (b) (4) used to prepare (b) (4)</p>			
<p>2. 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. For example:</p> <p>a. Failure to thoroughly investigate deviations. For example:</p> <p>i. Deviation 200183029 occurred on April 20, 2023, when a (b) (4) was incorrectly installed after (b) (4) Yimmugo lot (b) (4). An associated corrective and preventive action (CAPA) 200184757 was implemented to revise SOP-P-00135 "Description and operation of the (b) (4) line (b) (4) and the batch record to include the (b) (4) assembly on (b) (4) line (b) (4). Due to this CAPA, change control (b) (4) -2023-0494 was implemented to include a (b) (4) batch record. However, an investigation was not conducted to assess if any previous lots were affected by the incorrectly installed (b) (4) as the procedure did not describe how to correctly assemble the (b) (4) operators were not properly trained, and there was no (b) (4) for this step.</p> <p>ii. Deviation 200162802 initially occurred on August 30, 2021, when (b) (4) were observed during the evaluation of the (b) (4) of the (b) (4) of batch (b) (4), and a laboratory technician performing the test noticed unusual strong (b) (4) during mixing. However, an investigation into the root cause for the unusual (b) (4) of the (b) (4) was not performed, and a product quality impact assessment on the final drug product was not performed.</p> <p>iii. Deviation 200184454 initially occurred on May 21, 2023, when a (b) (4) contamination" was observed on the (b) (4) that is used to (b) (4) The (b) (4) contamination of</p>			
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the (b) (4) has been observed (b) (4) times since the initial occurrence, most recently on December 10, 2023. Analysis of the (b) (4) showed they are (b) (4). Since May 21, 2023, (b) (4) lots have been manufactured. A product impact analysis of the (b) (4) lots and a retrospective analysis of previous lots manufactured have not been performed.

b. The process to document and report deviations per SOP-S-00027 v. 6.0 "Deviation Management" is insufficient to demonstrate quality oversight of the manufacturing process. Specifically:

- There is no delineation to report deviations based on the incident criticality as all deviations must be registered within (b) (4). For example, a notification for a major deviation 200184454 was not issued within (b) (4).
- There is a lack of assurance that all deviations are recorded as only select individuals have system access to report deviations; deviations cannot be entered directly by manufacturing or laboratory staff.

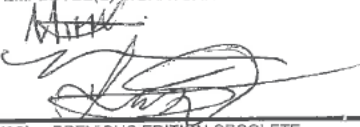
c. Quality review of documentation is inadequate. For example, in the report for deviation 200161793 that occurred on July 29, 2021, the incorrect root cause of the deviation was documented under the "Root Cause" section of the report even though the correct root cause was reflected in Attachment 10. Quality failed to identify the incorrect root cause and approved the deviation report.

3. Strict control is not exercised over labeling materials issued for use in the Yimmugo drug product labeling operations. For example, the labeling materials used to label Yimmugo 10%, 100 mL, lot (b) (4) on December 7, 2023, were (b) (4) on November 27, 2023, in room (b) (4) which can be accessed by over (b) (4) individuals including external contractors.

4. Procedures designed to monitor microbiological contamination are not established. For example, bioburden samples are not collected from (b) (4) such as the Yimmugo pH₂ treated (b) (4) and (b) (4) after (b) (4).

5. Manufacturing buildings used in the manufacture of Yimmugo do not have the suitable controls to prevent contamination. For example:

- There is no disinfectant efficacy study to support the use of (b) (4) surfaces. Specifically, (b) (4) did not provide a (b) (4) a facility (b) (4).

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b. Formulation room (b) (4) used in the manufacture of Yimmugo was not maintained in a qualified state for the open final formulation operation. Specifically, during the observation of the open final formulation operation, the door to (b) (4) did not fully close.

6. Manufacturing building (b) (4), where the Yimmugo drug product is manufactured, does not contain sufficient space to prevent mix-ups and to secure the product. For example:

a. Yimmugo drug product (b) (4) are (b) (4) in an (b) (4) (b) (4) where other drug products are concurrently (b) (4)

b. The Yimmugo drug product (b) (4) are labeled with the lot number (b) (4) crimp. This lot number can be removed from the crimp using a (b) (4) that is near the (b) (4)

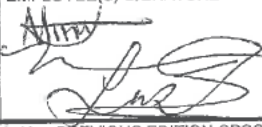
7. Process validation is deficient as it does not cover the proposed range for process parameters that are critical. For example, the (b) (4) range for (b) (4) which is used for the (b) (4) has not been validated. Batch record (b) (4)-00490 "Final (b) (4) pools IgG Next Generation (BT595) and (b) (4) without support of the (b) (4) specifies a (b) (4) range of (b) (4) however, on December 5, 2023, you stated that the (b) (4) is (b) (4).

8. Process controls are not established from validated manufacturing processes. Specifically, as a result of Deviation 200161821, the (b) (4) alarm during nanofiltration was modified to prevent an alarm from a (b) (4). The modified alarm permits the routine performance of the critical nanofiltration step to occur at (b) (4) which is (b) (4) the validated (b) (4) range for nanofiltration.

9. The manual visual inspection program is inadequate to identify (b) (4) matter and physical defects. For example:

a. Written procedures to fully inspect the crimping cap for defects are not established in SOP (b) (4)-00405 v. 12.0 "Implementation and test criteria for the visual inspection."

b. Employees engaged in the visual inspection of a drug product lack the training required to perform their assigned functions. Specifically, employees are not trained to fully inspect the product and crimping cap and, in the technique, to avoid (b) (4) that can interfere with the detection of (b) (4).

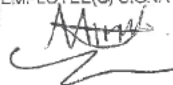
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<p>c. Qualification of visual inspection operators was not representative of the manual routine visual inspection procedure.</p> <p>10. The (b) (4) sampling process for routinely monitoring the (b) (4) is deficient. Chemical sampling for total organic carbon, conductivity, and nitrogen is (b) (4) bioburden sampling.</p>			
<i>MR</i> Dec 15, 2023			
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