DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
CBER/OCBQ/Division of Manufacturing and Product Quality 10903 New Hampshire Avenue, Silver Spring, MD 20993 Lead Insp.: Prajakta Varadkar Telephone: 240-402-7439 Industry Information: www.fda.gov/oc/industry	June 12-13 and June 16-20, 2025 FEI NUMBER 3001034985

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Dr. Jörg Schüttrumpf, Chief Executive Officer

FIRM NAME	STREET ADDRESS
Biotest AG, Germany	Landsteinerstraße 5, 63303 Dreieich, Germany
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Dreieich, Germany, 63303	DS and DP 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:

OBSERVATION 1:

Temporary deviations appear to be used to bypass quality system requirements for the Fibrinogen (Human) (BT524) DP manufacturing process. Per SOP-S-00027 "Deviation Management", temporary changes/deviations are to be opened in emergency circumstances and used as rarely as possible. It was found that numerous deviations have been opened in non-emergency circumstances, Specifically,

a. Temporary deviations (200201797, 200204345, 200210676; 200201818, 200201844, 2000202367, 200214472; 200203193, 200203498, 200214455, 200214456, 200214609, 200214671, 200214719) were opened for non-emergency recurring issues such as exceedance of calibration, exceedance of maintenance period, and grace period violation of system requalification.
b. Temporary deviations (200172032, 200176088 and 200177609), regarding plasma from an unqualified source, were pre-released without Plasma Master File Certification (PMF).
c. Temporary deviation (200198859) was opened for not testing in accordance with USP requirements for the following three incoming materials: (b) (4) (b) (4) The temporary deviation for sterile (b) (4) used as an excipient in the Fibrinogen DP, did not include an adequate product impact assessment.
d. Corrective and Preventive Actions (CAPAs) were not opened to address the prevention of recurring temporary deviations. Additionally, no trend analysis is performed on temporary deviations to evaluate historical data to identify patterns, shifts, or recurring issues.

OBSERVATION 2:

Written standard operating procedure SOP-S-00027 for "Deviation Management" lacks sufficient details related to:

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	Prajakta Varadkar Hoda Thai, Sergey Akimov	Prajakta Varadkar, Biological Reviewer, Lead Inspector Hoda Thai, Consumer Safety Officer Sergey, Akimov, Biologist	06/20/2025

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TO: Dr. Jörg Schüttrumpf, Chief Executive Officer	
FIRM NAME Biotest AG, Germany	STREET ADDRESS Landsteinerstraße 5, 63303 Dreieich, Germany
CITY, STATE AND ZIP CODE Dreieich, Germany, 63303	TYPE OF ESTABLISHMENT INSPECTED DS and DP Manufacturer

a. Reporting to regulatory authorities, depending on nature and impact of temporary deviations on product manufacturing.
b. Regulatory assessment/approval documentation or justification of the high-risk situation.
c. A clear timeframe for the temporary deviation and reassessment of its extension beyond the approved period.

OBSERVATION 3:

Aseptic control and cleanliness practices are inadequate. Specifically,

a. On June 18, 2025, during the observation of the set-up on filling line (b) (4) for DP manufacturing at Production Site (b) (4) Manufacturing Suite (b) (4) (Grade (b) (4), an operator was observed spraying disinfectant, inside the RABs, in close proximity to and around open (b) (4).
b. On June 12, 2025, during observation of open manipulation of the DS manufacturing process at Production Site (b) (4) Manufacturing Suite (b) (4) (Grade (b) (4), an operator retrieved an item that had been dropped on the Grade (b) (4) floor. After retrieving an item dropped on the floor, the operator did not change or sanitize their gloves and continued manufacturing operations. Per SOP-H-00090 "Personal- and Production Hygiene", operators are not allowed to reuse items dropped on the floor. Additionally, gloves and hand sanitizer are not provided in Manufacturing Suite (b) (4) (Grade (b) (4) where open manipulation of Fibrinogen DS manufacturing is performed. To change gloves, the operator must leave Manufacturing Suite (b) (4) and enter the (b) (4) room (b) (4) Room), where sterile gloves and other supplies are stored.
c. The operators in Weighing Suite (b) (4) (Grade (b) (4) at Production Site (b) (4) were observed opening trash bins with gloved hands and then proceeding to enter Manufacturing Suite (b) (4) (Grade (b) (4) without sanitizing or changing sterile gloves. Per SOP-H-00090 "Personal- and Production Hygiene", clean room operators are required to maintain adequate disinfection of gloves.
d. On June 12, 2025, containers used for (b) (4) were autoclaved, placed on a cart in (b) (4) Suite (b) (4) Grade (b) (4), and ready-to-use by manufacturing staff in Room (b) (4) (Grade (b) (4). One of the ungloved personnel proceeded to touch the outside of the sterilized autoclave overwrap without any gloves.
e. On June 12, 2025, during the (b) (4) in a Grade (b) (4) environment, gloved manufacturing staff and ungloved personnel were observed touching the same door handles to enter and exit the (b) (4) Suite (b) (4), Manufacturing Suite (b) (4), and (b) (4) Suite (b) (4), without disinfecting in-between.

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OBSERVATION 4:

Procedures are not established to prevent loss of containment. Specifically, On June 19, 2025, during filling of the Fibrinogen DP at Production Site (b) (4) Manufacturing Suite (b) (4) (Grade (b) (4)). We observed that there was an incidence of leakage during Fibrinogen DP filling for batch (b) (4). Droplets were seen leaking from the (b) (4). However, the spill was not observed by operators and was not cleaned immediately per SOP-H-00118 "Cleaning Measures in Final Filling/Final Product (b) (4)." In addition, there are no records of checks or verifications performed for leakage after the (b) (4) (b) (4).

OBSERVATION 5:

Facilities and equipment used in the manufacture of Fibrinogen are not in a state of good repair or are in a state of uncleanliness. Specifically,

a. On June 12, 2025, paint chipping was observed in the (b) (4) in, Production Site (b) (4), Manufacturing Suite (b) (4) while (b) (4) was being performed via (b) (4).
b. On June 12, 2025, in Production Site (b) (4) Manufacturing Suite (b) (4), dry residue was observed underneath where the (b) (4) were hung.
c. On June 12, 2025, in Production Site (b) (4) Manufacturing Suite (b) (4), rust and residue were observed on the (b) (4) of the Grade (b) (4) area.
d. On June 12, 2025, in Production Site (b) (4) Room (b) (4) (Grade (b) (4)) cracks were observed on the floors.
e. During observation of (b) (4) of the DS manufacturing process at Production Site (b) (4) Manufacturing Suite (b) (4) (Grade (b) (4)) on June 12, 2025, visible residue was observed on the lid of an (b) (4) (b) (4). The addition of (b) (4) is performed via an (b) (4) step during Fibrinogen (Human) (BT524) DS manufacturing.
f. Centrifuges used for the purification of Fibrinogen DS intermediates by (b) (4) treatment, located in Manufacturing Suite (b) (4) (Grade (b) (4)), showed visible spots on various surfaces.
g. Additionally, documentation of equipment cleaning in (b) (4) Suite (b) (4) (Grade (b) (4)) is not performed.

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Preventative maintenance of major equipment is inadequate. The following observations were made:

a. On June 12, 2025, during the (b) (4) in Production Site (b) (4), Manufacturing Suite (b) (4), and (b) (4) Room (b) (4) the following observations were made:
i. Rust on the centrifuge(s) and chipping along the seam (Equipment ID: (b) (4)). Additionally, the connection from the top of the centrifuge to the monitoring system appeared to have a thick build-up of cracking paint (Equipment ID: (b) (4)).
ii. Rust deposits on the surface underneath the (b) (4) of the centrifuge (Equipment ID: (b) (4)).
iii. Rust along the lid of the (b) (4) Production Vessel (Equipment ID: (b) (4)).
iv. Metal shavings on the pump of the (b) (4) Vessel (Equipment ID: (b) (4)).
b. On June 16, 2025, during inspection of the (b) (4) Warehouse (Building (b) (4)), it was observed that the (b) (4) freezer (Equipment ID: (b) (4)) had ice build-up and visible condensation surrounding the edges and the floor.

OBSERVATION 7:

Facility cleaning validation and disinfectant efficacy studies are inadequate. Specifically,

a. Per SOP-H-00136 "Cleaning and Disinfecting Agents at the Site" (b) (4) and (b) (4) (b) (4) disinfectant agents used in Grade (b) (4), do not demonstrate effectiveness against all representative surfaces in areas (b) (4) used to manufacture Fibrinogen DP. Additionally, (b) (4) disinfectant used in Grade (b) (4) was not included in the disinfectant efficacy studies.
b. Validation of Cleaning and Disinfectant Processes in cleanrooms Grade (b) (4) per (b) (4) included testing of just (b) (4) using (b) (4) and did not include other commonly challenged microorganisms or facility isolates.
c. Validation studies (b) (4) and Validation studies (b) (4) disinfectant efficacy studies leveraged for facility cleaning validation, did not include frequently found facility isolates in Grade (b) (4) areas.

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OBSERVATION 8:

The design of the Fibrinogen activity assay is deficient. Specifically, the in-house Fibrinogen (Human) reference material that has not been calibrated against a current International Standard for Fibrinogen.

Dates of inspection:
June 12, 2025 (Thursday), June 13, 2025 (Friday), June 16, 2025 (Monday), June 17, 2025 (Tuesday), June 18, 2025 (Wednesday), June 19, 2025 (Thursday) and June 20, 2025 (Friday).

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or

2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."