DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Division of Pharmaceutical Manufacturing Assessment 10903 New Hampshire Avenue; White Oak Building 51, Room 2269, Silver Spring, MD 20993 Email: OPMABLAInspection483Responses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	02/10 - 18/2025 FEI NUMBER 3004110157

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Stefano Chiaramonti, Vice President & General Manager Pharma Services

FIRM NAME	STREET ADDRESS
Thermo Fisher Scientific (Patheon Italia S.p.A.) 4/10/25	2 Trav. SX Via Morolense 5
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Ferentino, Italy 03013	Drug Product Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

Observation 1:

Quality Unit (QU) oversight over the manufacturing process is inadequate. Specifically,

A. Written records of investigations into unexplained discrepancies, the failure of a batch or any of its components to meet specifications, do not always include appropriate documentation, conclusions, and follow-up. For example,

a. No deviation record was opened for the use of an unqualified standard and procedure for reinspection of (b)(4) lot of (b) (4) (100% (b) (4) VI) on 11 September 2024. The same lot was subjected to another 100% (b) (4) VI (second reinspection) between 25 - 27 September 2024. No deviation was opened for exceedance of the maximum number of reinspections (b) (4) allowed per your procedure SOP-000042781, "Procedura generale di ispezione visiva", ver.19.

b. You were informed by your client on 29 January 2024 that the validated filling time duration for (b) (4) should be reduced to that validated via (b) (4) media fills, i.e., (b) (4) Although this time was exceeded for (b)(4) and (b)(4) batches, no deviation record was created to investigate the root cause and product impact of this event.

c. Instrument (b) (4) the plate reader used for in-process control and DP release endotoxin testing had a Certificate of Calibration, dated 27 November 2024 with the as found condition for the (b) (4) nm and (b) (4) nm A/D values (tubes absent) out of tolerance. You failed to conduct a deviation investigation for the out of tolerance event.

d. Your QU does not verify that microbial sample testing of (b) (4) DS and DP is performed within the sample's defined expiry date. Specifically,

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• Your study MVD-000565037, "R-QCB-LER HT study on (b) (4) ver.2 validated sample storage duration o(b) (4) at (b) (4) C. MET-000492422 ver.01 logbook documenting sample testing and outcomes does not include record of endotoxin in-process and release sample collection date; as such duration of sample storage prior to testing cannot be verified.

• Although date of in-process bioburden sampling is included in MET-000607812 ver.01 logbook documenting sample testing and outcomes, sample hold duration is not calculated and verified. As such, there is no assurance that the testing is performed within (b) (4) of sampling.

As such, validity of the outcomes of (b) (4) testing results cannot be assured.

B. Your QU does not have adequate control over the sets used for qualification of personnel performing (b)(4) visual inspection (b) (4) VI). For example,

a. The qualification sets are stored in the warehouse, from where they can be requested by the production department, without notifying the QU. During the tour of the Warehouse (b) (4) on 13 February 2025, qualification sets for (b) (4) glass vials (b) (4) were observed in an unsecured state.

b. Qualification sets checked out by the production department are stored in the visual inspection room, where they can remain for extended periods of time. For example,

- (b) (4) glass vial (b) (4) set was checked out of the warehouse on 08 October 2024, checked in on 26 October 2024 (18 days)
- (b) (4) set was checked out of the warehouse on 08 November 2023, checked in on 13 June 2024 (218 days)
- (b) (4) set was checked out of the warehouse on 03 September 2024, checked in on 05 December 2024 (93 days)

c. Per your SOP-000042781 "Procedura generale di ispezione visiva", ver.19, section 5.2.4, each defective unit of a qualification set can contain (b) (4) defect. I (EA) observed that the (b)(4) qualification kit included (b) (4) with multiple visual defects. Specifically, defects (b)(4) (fiber), (b)(4) (particle), and (b) (4) (bent stopper (b) (4) additionally included incorrect (b) (4) defect. Your QU failed to ensure that defective units contain individual visual defects.

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d. Your QU failed to ensure that all integral media-filled units from aseptic process simulations (APS) are incubated, as it does not perform independent verification of non-integral vials rejected by production operators. QU oversight of media fill readout performed by production operators is limited to confirmation of contaminated units. No independent readout is performed.

Observation 2:

Failure to establish process controls and testing designed to assure that the drug products you manufacture have the identity, strength, quality and purity that it purports or is represented to possess. Specifically,

a. Your firm failed to adequately validate and control the stoppering process for (b) (4) bulk (b) (4) Specifically,

No engineering runs were performed prior to (b) (4) to establish the critical process parameter (CPP), (b) (4) (b) (4) necessary to ensure that (b) (4) meets the specification of NLT (b) (4) batches were manufactured at a (b) (4) with an alarm set at (b) (4) From (b) (4) bulk (b) (4) units were sent to the (b) (4) of which (b)(4) units (b) (4) %) failed the (b) (4) check. Your QR 847868 deviation investigation into the matter concluded that frequent stoppages during the batch led to an increased (b) (4) variability. However, this potential source of variability of the CPP could not be confirmed as the (b) (4) was not recorded in the executed MBR or (b) (4) batch report for any of the PPQ batches. As such, there is no assurance that the source and extent of the (b) (4) variability are identified and this CPP is adequately controlled.

In addition, your deviation investigation did not document the comparative assessment of the number of stoppages during (b) (4) where (b) (4) was controlled.

b. Packaging for the (b)(4) fill line stoppering system for (b) (4) sterilization by (b)(4) includes a (b) (4) cover over the equipment and a (b) (4) The (b) (4) you use includes a (b) (4) that has not been evaluated by risk assessment for impact on product quality.

Furthermore, on 12 February 2025, a (b) (4) packaged stoppering system component (b) (4) in the (b)(4)

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(b) (4) fill line pending (b) (4) for manufacture of (b) (4) batch (b)(4) was observed with a (b)(4) stain on the outside of the (b) (4) packaging. SOP-000316846, "Check-list di allestimento (b)(4) Sterile (b) (4), fails to provide adequate instruction for visual inspection of packaging for its fit for manufacture (absence of staining).

c. On 10 February 2025, (b) (4) bottles of (b) (4) drug substance (DS) were observed stored within the (b) (4) 2 - 8C refrigerator (b)(4) under indirect light conditions. The (b) (4) DS label instructs to protect from light. You failed to assure the (b) (4) DS is stored under appropriate conditions.

Observation 3:

Procedures designed to prevent microbiological contamination of drug product purporting to be sterile are not fully established or followed. Specifically,

a. Your manufacturing process for fill lines (b) (4) includes (b) (4) for U.S. commercial manufacture of (b) (4) In the aseptic process simulation (APS) for the specified fill lines, you failed to replace (b) (4) (b) (4) for the (b) (4) system and as a (b) (4) on fill line (b) (4) is used as a (b) (4) only). The APS is not representative of your commercial manufacturing process as you failed to have the (b) (4) system active during media fills.

Although you recognized the deficiency in August 2023 and the opened CAPA to include the addition of (b) (4) (b) (4) to each of the specified fill lines for replacement of (b) (4) for the (b) (4) system and (b) (4) n the APS, its implementation is currently scheduled for January 2026. You failed to conduct corrective action in a timely manner.

b. Qualification and periodic requalification of aseptic operators does not require performing all routine interventions during APS. For example, of the (b)(4) aseptic operators qualified to perform a critical routine intervention of the (b) (4) installation of stopper parts, only (b) (4) operators performed it during APS. The current minimal requirement for the number of interventions used for qualification of an individual operator (b) (4) high risk intervention and (b) (4) medium risk intervention, no requirement for performance of any routine

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interventions) outlined in SOP-000215814, "QAC-Qualifica del personale per le aree classificate", ver.5, is not supported by a risk assessment.

c. On 12 February 2024 during the (b) (4) fill line (batch (b) (4) setup and subsequent (b) (4) intervention for removal of the (b) (4) covers from the stoppering system (b) (4) decontamination), an operator was observed touching the surface of the sterile stopper (b) (4) with the non-sterile (b) (4) during removal of the (b) (4) cover from the stopper bowl.

Sterility of equipment used for aseptic operations was not maintained in assurance of product sterility.

d. On 13 February 2025, the mounting of the (b) (4) sterile (b) (4) to the (b) (4) for the (b) (4) (b) (4) fill line was observed for (b) (4) manufacture, batch (b)(4) During mounting of the (b) (4) the drug product (b) (4) tubing (b) (4) of the bagged and protected (b) (4) was touched by sanitized (b) (4) rather than another sterile instrument or equivalent approach.

Additionally, the (b) (4) mounted directly above the open (b) (4) is not sterilized prior to filling operations.

Observation 4:

Your program for the visual inspection of sterile (b) (4) drug products does not provide adequate assurance that finished products manufactured at your facility possess their purported quality attributes, including that they are essentially free from particulate matter. This is evidenced by:

A. Training and qualification of personnel performing (b) (4) visual inspection (b) (4) VI) of small volume parenteral products filled in (b) (4) glass vials (b) (4) are inadequate. Specifically,

a. Per SOP-000042781, "Procedura generale di ispezione visive", ver. 19, training of visual inspectors consists of theoretical training on visual (b) (4) VI-related procedures, review of the photo library of defects, and on the job training with a qualified inspector. You do not have training visual inspection sets for familiarization of inspectors with the defects they may encounter while performing (b) (4) VI and you failed to provide evidence that the required

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on the job training is being performed.

b. Prior to inspector qualification, the qualification supervisor pulls out defective units from the qualification set and shows the defects to the candidate visual inspector(s). The units in the set are identified with black ink numbers on the (b) (4) cap. As such you cannot assure that your kit remains blinded to the candidate visual inspector.

c. The bracketing strategy used for qualification of the visual inspectors is not scientifically justified as it does not always consider the challenge to the visual inspection presented by the product fill volume, viscosity, or optical properties of the primary container closure system. For example,

i. Visual inspectors of (b) (4) drug product filled into a (b) (4) at a target fill volume of (b) (4) mL are qualified using a set containing (b) (4) of such (b) (4) filled with (b) (4) mL of (b) (4) Remaining (b) (4) in the set are (b) (4) units of (b) (4) mL glass (b) (4) filled with (b) (4) mL of (b) (4) Consequently, the qualification set contains only (b) (4) defects (including (b) (4) particle and (b) (4) fiber defects) in the (b) (4) representative of (b) (4) presentation; and does not include several critical defects, e.g., (b) (4) internal scratches, non-compliant volume, etc.

ii. Visual inspectors of drug products filled in (b) (4) glass vials (b) (4) ranging from (b)(4) (all fill volumes) are qualified using the set containing (b) (4) glass vials (b) (4) contains (b)(4) (b) (4) mL fill) and (b) (4) mL fill) vials filled with (b) (4) You manufacture (b) (4) commercial U.S. drug products that are included within this bracket despite their fill volume exceeding (b) (4) mL. Additionally, you do not document assessments determining whether a new product being introduced into the facility can be included in the bracket, unless a product-specific visual inspection qualification set needs to be created. For example, no evidence of assessment was provided for product (b) (4)

d. Selection of particle and fiber defect types that were included in qualification sets and the (b) (4) set used for probability of detection (PoD) determination is not supported by a risk assessment. Your material assessment of potential (b)(4) area contaminants identified (b) (4) types of fibers and (b) (4) types of particles. There is no assurance that they are adequately represented in the sets.

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e. [redacted] glass vial [redacted] qualification sets do not include units with fiber defects at the detection level threshold, i.e., ~[redacted] µm.

f. You did not perform [redacted] studies supporting adequate PoD during [redacted] VI of [redacted] The [redacted] study performed for [redacted] vials filled with [redacted] mL of [redacted] did not consider the range of product viscosities, fill volumes, and container types it is intended to represent. Furthermore, inspectors were instructed to examine each vial for up to [redacted] which is not representative of your [redacted] VI process as the minimum allowed inspection time according to your work instruction WI-000620064, "Modalita operative per [redacted] ver. 1 is [redacted]

g. [redacted] VI threshold limits established during the PoD study show that your inspectors can detect fibers within the range of [redacted] µm with a probability of [redacted] % [redacted] and [redacted] % [redacted] The outcomes of the PoD study do not support that the [redacted] VI process can adequately detect fiber ranges [redacted] µm with a PoD of [redacted] % or greater.

h. During observation of the 100% [redacted] visual inspection of lot [redacted] of [redacted] the following was noted:

- The operators were shaking vials to suspend potential particles in a manner that generated bubbles.
- The operator picked up the vial dropped on the [redacted] VI booth table and placed it with the rest of the uninspected vials. According to your SOP-000042601, "Modalita operative d'ispezione visiva [redacted]", ver. 43, any fallen vials should be immediately rejected and tracked as fallen vials in the batch record. You failed to follow the procedure.

B. Your firm has not established adequate process control for commercial [redacted] bulk [redacted] This is evidenced by:

a. You have not validated the inspection process to measure the [redacted] the [redacted] mL [redacted] during the aseptic filling [redacted] in-process check, and the [redacted] visual inspection process. Appropriate threshold (sensitivity) studies have not been conducted to demonstrate your firm's visual inspection process capability to remove the [redacted] with [redacted] of less than [redacted] from the [redacted] finished product. Furthermore, your [redacted] visual inspection qualification kit does not include a [redacted] defect at the

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threshold of detection.

b. You did not qualify the minimum visual inspection time allowed per work instruction WI-000620064, "Modalita operative per (b) (4) ver. 1. Although inspection duration of (b) (4) (b) (4) is allowed, a duration of up to (b) (4) during visual inspector qualification is considered acceptable.

C. The (b) (4) visual inspection environment is not designed to ensure optimal inspection performance. The visual inspection booths are placed side by side, without any separation and adjacent to refrigerator PDS397. There is no assurance that an inspector can adequately perform (b) (4) VI without being distracted by the work activities inside the room, such as machinery noises and operator movement.

D. The AQL sampling strategy is not fully documented in the (b) (4) manufacturing batch record. Specifically, the calculation of the total sample size distribution between the specified number of (b) (4) sampled from (b) (4) is not documented and verified.

Observation 5:

Your program for the environmental control of classified areas, including critical supporting area for the Grade A (b) (4) does not provide assurance of your ability to adequately clean and/or disinfect your classified areas and detect levels of their microbial contamination. Specifically,

A. Your routine environmental monitoring (EM) program is not optimized for detection of environmental contaminants and monitoring the state of your manufacturing facility. For example, floor viable surface sampling in all classified areas of the (b)(4) facility is limited to sampling points (b) (4) (b) (4) Walls of the facility are not routinely monitored.

B. Your procedures for cleaning of the classified areas are either deficient or not followed. For example, per SOP-00382550, "(b) (4) Pulizia locali classi C e D Reparto (b)(4) ver.4, "(b) (4) cleaning" should be performed (b) (4) in the absence of production activities and (b)(4) cleaning with sporicidal should be performed (b) (4) (b) (4) According to the cleaning log (b) (4) 049/02-10 (filling room (b)(4) and associated (b) (4) no

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(b)(4) cleaning was performed (b) (4) Additionally, the maximum number of (b) (4) allowed between cleanings is not defined in the SOP.

C. Your Environmental Monitoring Process Qualification (EMPQ) performed concurrently with APS runs in (b) (4) (b) (4) (vial filling process) and (b) (4) filling process) did not challenge the maximum occupancy of room (b) (4) people) throughout the duration of EMPQ sample collection. Specifically, no passive or active air sampling was performed during maximum occupancy challenge associated with APS runs (b)(4) During APS run (b)(4) all (b) (4) people were present for (b) (4) out of (b) (4) of passive viable air sampling duration; no concurrent active air sampling was performed.

D. Disinfectant efficacy studies do not support the intended use of the cleaning reagents at the (b)(4) facility. For example,

a. You did not perform disinfectant efficacy studies at the end of their assigned post-opening expiry date. As such, there is no evidence that any of the disinfectants/sporicidals used in (b)(4) facility retain their bactericidal, fungicidal, and sporicidal activity through the assigned expiration date under the conditions of use (e.g., facility-specific surfaces, validated contact time, etc.).

b. You do not perform facility surface assessments to ensure that effectiveness of disinfectants is appropriately validated for all applicable surfaces of your facility upon their introduction. For example, disinfectant effectiveness study FR-VP-3095-01 rev. 00 issued April 2015 validated (b) (4) effectiveness using in-house isolates only and was limited to (b) (4) surfaces. No additional disinfectant effectiveness study was performed until 2023 despite (b) (4) being widely used throughout the facility, for cleaning of (b) (4) (b) (4) surfaces.

The supplemental study report STUIZ23AA0047-2, "Evaluation of the bactericidal/ fungicidal activities on surfaces", v1, approved 18 May 2023 did not challenge (b) (4) effectiveness using in-house isolates from your facility.

Observation 6:

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An equipment system in support of (b) (4) drug product manufacture failed to function satisfactorily and is not routinely verified. Specifically,

A. The (b) (4) fill line (b) (4) failed to operate continuously without fill line stoppage. Eight such events occurred during manufacture of two batches.

B. Performance of (b) (4) used in (b)(4) department for (b) (4) of the (b) (4) drug product on the (b) (4) fill line was validated for (b) (4) in the range of (b) (4)% to (b) (4)%, with the theoretical to measured difference for (b) (4) tolerance ≤(b) (4)%. You do not verify at any interval that the (b) (4) output continues meeting the acceptance criteria to assure the qualified/validated state is maintained.

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