DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	5/18/2023-5/26/2023*
	FEI NUMBER 3003065803

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Vincent Hingot, VP Drug Product Division EU & APAC

FIRM NAME	STREET ADDRESS
Patheon Italia S.p.A.	Viale Gian Battista Stucchi 110
CITY, STATE, ZIP CODE, COUNTRY Monza, Monza E della Brianza, 20900 Italy	TYPE ESTABLISHMENT INSPECTED Sterile Drug 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 WE OBSERVED:

OBSERVATION 1

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically, the firm did not implement effective mitigative actions after repeated adverse trends were identified from microbial testing.

(A) In 2021, the firm identified 3 adverse trends associated with personnel monitoring (PM). In 2022, 5 adverse PM trends were identified. From February 2023 to April 2023, the firm had 6 adverse PM trends despite implementation of two improvement initiatives in the first quarter of 2021 and three improvement initiatives in the first quarter of 2022.

(B) Beginning in September of 2022, the firm observed an increase in adverse environmental monitoring (EM) trend mostly associated with samples collected from the (b) (4) locations in the cleanroom. This adverse trend continued into April 2023. The firm did not implement an interim mitigation action by increasing the frequency of the cleanings with sporicidal agent from (b) (4) to (b) (4) until March 13, 2023.

OBSERVATION 2

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written and followed.

Specifically, the media fills for Sterile Area (b) (4) and Sterile Area (b) (4) simulating the manufacturing process of (b) (4) parenteral vial products were executed using a (b) (4) approach of vial opening size of (b) (4) mm and (b) (4) mm. A comparison of the specifications for the vials used in the production of (b) (4)

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	Mindy M Chou, Investigator Brandy N Lepage, Investigator	X Mindy M Chou Investigator Signed By: 2000648922 Date Signed: 05-26-2023 18:50:42	5/26/2023

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(b) (4) Injection, (b) (4) mg/vial and the vials used in the executed media fills is summarized below:

	(b) (4) Sterile Are (b) (4) Media Fill	Sterile Area (b) (4) Media Fill
Filling Line	(b) (4)	(b) (4)
Dosing System		
(b) (4)		
Fill Volume (Target)		
Nominal Capacity		
Vial Overall Height		
Vial Body Diameter		
Vial Opening Diameter		
Vial Code		

The firm's media fill design is governed by SOP-000026985, La simulazione del processo asettico: Media Fill. The firm's written document did not provide scientific justification for the following statement:

- A difference in the size of (b) (4) is not in itself considered a relevant factor in determining the "worst case".
- The diameter of the body and height of the container are not generally considered relevant.

Additionally, (b) (4) Injection, (b) (4) mg is filled using a (b) (4) However, the comparable vial used in the media fill study is performed using a (b) (4) Neither the media fill study protocol, nor SOP-000026985 contain scientific justification which explains how a media fill study filled using a smaller vial (b) (4) mL), with a vial opening diameter (b) (4) mm), and a different dosing system (i.e., (b) (4) is

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considered a closely simulated aseptic manufacturing operation with the worst-case conditions, compared to the (b) (4) commercial manufacturing process.

OBSERVATION 3

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use.

Specifically, the equipment qualification for (b) (4) Leak Integrity Tester (Equipment ID # (b) (4) 002) executed under Protocol Document # FPS0364COQ01 was performed without any pre-defined procedure on how the breached (b) (4) used during the qualification was made to test the equipment's capability of consistently and reliably detecting a leak in the restricted access barrier system (RABS) (b) (4) Additionally, the established acceptance criterion for the integrity test is no pressure loss of (b) (4) in (b) (4) The firm has not calibrated the equipment timer to ensure the accuracy of the timer. This (b) (4) Leak Integrity Tester is used in testing the RABS (b) (4) used in the manufacturing of sterile drug products such (b) (4) Injection, (b) (4)(b) (4) /vial in Sterile Area (b) (4) and Sterile Area (b) (4)

OBSERVATION 4

Drug products are not stored under appropriate conditions of temperature so that their identity, strength, quality, and purity are not affected.

Specifically, your warehouse, which is used to store active pharmaceutical ingredients and finished drug products that have controlled room temperature labeled storage conditions, was not qualified using scientific-driven temperature mapping studies. The studies did not include the collection of temperatures at all representative warehouse locations where APIs and drug products with labeled storage conditions are stored.

- The winter seasonal study executed under the report titled, "Periodical mapping Temperature and Relative Humidity - Intensive Warehouse - HVAC CDZ040 - Winter season 2023," conducted between 02/23/2023- 03/02/2023 utilized (b) (4) probes which were located at the heights of (b) (4) however, only (b) (4) probes were placed at the (b) (4) height and were located exclusively within one row,

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in the (b) (4) of the warehouse.

- The summer seasonal study executed under the report titled, "Verifica periodica PQ - Magazzino intensivo - CDZ040," conducted between 08/22/2018-08/29/2018 utilized (b) (4) probes which were located at the heights of (b) (4) with zero probes placed at the (b) (4) height.

***DATES OF INSPECTION**

5/18/2023(Thu), 5/19/2023(Fri), 5/22/2023(Mon), 5/23/2023(Tue), 5/24/2023(Wed), 5/25/2023(Thu), 5/26/2023(Fri)

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Investigator
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Date Signed: 05-26-2023 18:51:23

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