DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
60 Eighth Street NE Atlanta, GA 30309 (404)253-1161 Fax:(404)253-1202 ORAPHARM2_RESPONSES@fda.hhs.gov	5/15/2024-5/24/2024* FEI NUMBER 1018495

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Thomas Schornak, General Manager and Vice President

FIRM NAME	STREET ADDRESS
Patheon Manufacturing Services LLC	5900 Martin Luther King Jr Hwy
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Greenville, NC 27834-8628	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:
PRODUCTION SYSTEM

OBSERVATION 1

Your firm failed to establish written procedures for production and process controls designed to assure that the drug products have the identity, strength, purity, and quality that they are purported or represented to possess.

Specifically,

A. Your firm have not established adequate process controls for commercial (b) (4) (b) (4) (b) (4) syringes ((b) (4) and (b) (4)). This is evidenced by the following:

i. You have not qualified the inspection procedures to measure the size of air bubbles inside the (b) (4) and (b) (4) ((b) (4)) during the aseptic filling/stoppering in-process check, and the 100% (b) (4) or (b) (4) visual inspection processes. Appropriate threshold studies have not been conducted to demonstrate your firm's visual inspection process capability to remove the syringes with air bubbles greater than (b) (4) from (b) (4) finished product manufactured at your facility.

ii. You have no documented scientific justification for the sampling frequency ((b) (4) for (b) (4) batches manufactured prior to August of 2023 and approximately (b) (4) for batches manufacture since August of 2023) for the bubble size in-process monitoring during

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the aseptic filling/stoppering operation. Your sampling plan for bubble size do not result in statistical confidence in your process performance. In addition, your in-process control is not designed to allow for adjusting the processing conditions in response to any test failures to assure quality of the product. For example, during the filling of (b) (4) air bubble size in-process check inspections failed the (b) (4) syringe check. In each instance an additional (b) (4) syringes were inspected and the manufacturing continued to completion with no investigation on the manufacturing process.

B. Your firm has not fully validated the manufacturing process for (b) (4) (b) (4) (b) (4) ((b) (4) and (b) (4)). After review of the process performance qualification study ((b) (4) and (b) (4)) (MVD-000182700, version 5.0, approved 22 May 2023), the following deficiencies were identified indicating your process is not robust:

i. Lack of evaluation of the failures that lead to three (3) of the (b) (4) batches that exceeded critical defect limit of (b) (4):

(b) (4)	Critical Defects	(b) (4)	Critical Defects
	(b) (4)		(b) (4)

Additionally, the critical defects evaluated in this PPQ validation does not include the evaluation of the bubble size control measurement of greater than (b) (4).

ii. Lack of evaluation of the impact of the stoppering (b) (4) on the "liquid in plunger" critical defect. (b) (4) consecutive (b) (4) batches, (b) (4) and (b) (4), exceeded the critical defect action limit of (b) (4) with (b) (4) and (b) (4) which consisted of "liquid in plunger" critical defects (QR 624424 & QR 632662).

C. Your program for the visual inspection of sterile injectable drug products does not provide

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adequate assurance that finished products manufactured at your facility possess their purported quality attributes, including that they are free from particulate matter. This is evidenced by:

i. While observing AQL inspection of (b) (4) (b) (4) (Batch # (b) (4)) on May 16, 2024, your QA inspector was observed inspecting for particulates by holding (b) (4) syringes in position for approximately (b) (4) in front of the (b) (4) . While observing a demo of manual inspection of (b) (4) syringes ((b) (4) (b) (4) and (b) (4)) on May 17, 2024, your inspector was observed inspecting for particulates by holding (b) (4) syringes in position for about (b) (4) in front of the (b) (4) (b) (4) . You have no studies to support this timeframe is adequate for particulate detection.

ii. While observing AQL inspection of (b) (4) (b) (4) (Batch # (b) (4)) on May 16, 2024 and the demo of manual inspection of (b) (4) syringes ((b) (4) and (b) (4)) on May 17, 2024, both inspectors were observed (b) (4) syringes (b) (4) to inspect plunger defects (including particulates and liquid in the plunger). SOP-000062512 "Syringe Manual Inspection Operations" (version 5.0, effective 13 Mar 2024) does not specify the (b) (4) amount of time required to inspect these critical plunger defects.

iii. Your firm's manual visual inspection threshold limits established within a (b) (4) for (b) (4) , (b) (4) fill volume, MVD-000209431, (version 1.0, approved 01 Jun 2022), shows that your firm's inspectors can detect particulates within the range of (b) (4) (b) (4) with a probability of detection (PoD) of (b) (4) and fibers within range of (b) (4) (b) (4) with a PoD of (b) (4). You do not have scientific rationale to support your manual visual inspection thresholds established can adequately detect particulate ranges of (b) (4) (b) (4) ((b) (4) for fibers) with a PoD of (b) (4) .

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D. Your firm failed to implement an adequate on-going program for (b) (4) ((b) (4)) (b) (4) syringes ((b) (4) and (b) (4)) to monitor process control to ensure consistent manufacturing operations and consistent drug quality. Your quality unit failed to collect and analyze product and process data that relate to product quality. Since February of 2023, a total of (b) (4) post-PPQ commercial batches have been manufactured at your (b) (4) manufacturing facility.

OBSERVATION 2

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

Specifically,

A. Indirect product-contact parts, including the (b) (4) stoppering system ((b) (4) and (b) (4) (b) (4)) and stopper (b) (4) , are not sterilized prior to assembly in the (b) (4) before each (b) (4) filling operation.

B. Sterilized indirect product-contact parts including stopper (b) (4), stopper (b) (4) and stopper (b) (4) (b) (4) are removed from the (b) (4) and exposed to the Grade (b) (4) (in operation) environments outside the (b) (4) prior to the loading and installation of the parts inside the Grade (b) (4) .

C. While observing the filling operations on the (b) (4) for the filling of (b) (4) (b) (4) (b) (4) (batch# (b) (4)) on 16 May 2024, the following deficiency was noted:

i. While performing stopper addition, the operator blocked (b) (4) to the stoppers within the (b) (4) with a non-sterile (b) (4) glove and (b) (4) port. In

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addition, the (b) (4) glove made direct contact with the stoppers entering the (b) (4), stopper (b) (4), the (b) (4).

D. While reviewing the (b) (4) Smoke Study videos (MVD-000498121), version 1.0, approved 30 Apr 2024) for the (b) (4), the following deficiencies were noted:

i. While installing the stopper (b) (4), stopper (b) (4), and stopper (b) (4), the operator touched the sterilized parts with their gloved hands.

ii. While installing the stopper (b) (4), the operator blocked (b) (4) over the exposed sterile surfaces of stopper (b) (4) with the non-sterile stopper (b) (4) (b) (4).

iii. While removing the inner (b) (4) from stopper (b) (4) and stopper (b) (4), the operator blocked (b) (4) over the exposed sterile surfaces of these indirect product-contact equipment with the non-sterile (b) (4).

iv. While installing/replacing/adjusting the filling needles, stopper (b) (4), and (b) (4) (b) (4), the operator blocked (b) (4) over the exposed filling needles and stopper (b) (4) openings with the non-sterile (b) (4) glove.

v. While changing out environmental monitoring plates using (b) (4) glove 8, the operator touched the stopper rack with the non-sterile (b) (4) glove. In addition, while removing the jammed stoppers in stopper (b) (4), the operator blocked (b) (4) over the stoppers in the stopper rack with the non-sterile (b) (4) glove.

E. During the filling operation of (b) (4) Batch (b) (4) on May 24, 2023, an unqualified intervention was performed by maintenance to clean (b) (4), stopper (b) (4) (b) (4) and stopper (b) (4) with (b) (4) wipes. There was no (b) (4) decontamination cycle performed on the (b) (4) prior to restarting the aseptic filling/stoppering process.

F. Environmental monitoring (EM) of aseptic processing areas for the below aseptic filling operations were found deficient. For example:

i. During routine EM following aseptic filling activities, not all (b) (4) gloves are sampled. Microbiological surface samples are only taken from (b) (4) gloves that are used on the aseptic filling line. Additionally of the glove sampling performed, (b) (4) glove (b) (4) samples are taken which does not represent the entire (b) (4) used during aseptic filling operation. Since July 2022, your firm generated approximately 35 glove integrity testing failures during filling operations, with six (6) of them impacting (b) (4) products. With the exception of one batch, all other (b) (4) products have been released for commercial distribution.

ii. During the routine EM following the filling activities, microbiological surface samples were only taken from (b) (4) filling needles.

G. Your firm lacks an established cleaning and sanitization program to prevent the introduction of microbial contamination into controlled sterile (b) (4) manufacturing environments. In particular, your cleaning and sanitization procedure for the manufacturing areas in the (b) (4) (SOP-000062487, version 7.0, effective 22 Oct 2023) does not do not require the documentation and verification that the treated surfaces are (b) (4) and remain (b) (4) for the contact time validated in the disinfectant efficacy studies, in the cleaning logbooks during the facility cleaning and sanitization.

OBSERVATION 3

Written records of investigations into do not include the conclusions and follow-up.

Specifically,

A. Deviation QR-614139 was initiated for exceeding the PPQ target defect rate acceptance criteria of (b) for (b) (4) (b) (4) during (b) (4) visual inspection ((b) (4)) process PPQ for inspection of commercial batch (b) (4). During the investigation, it was discovered that the

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following batches underwent a (b) (4) visual inspection ((b) (4)) process that did not include the inspection of bubble size using the (b) (4) inspection fixture:

PPQ Batches: (b) (4)

Stability Batches: (b) (4)

Commercial Batches: (b) (4)

Your firm's investigation failed to conduct a thorough product impact assessment for the above batches. There is no assurance that the syringes with air bubble sizes (b) (4) had been removed from these commercial batches during the manufacturing process.

B. Deviation QR-635673 was initiated on August 31, 2023 to investigate the recurring critical defect limit ((b) (4)) excursions for the following (b) (4) batches:

(b) (4) (QR-624424): exceeded Critical Defect Limits for Liquid in Plunger at (b) (4)

(b) (4) (QR-632662): exceeded Critical Defect Limits for Liquid in Plunger at (b) (4)

(b) (4) (QR-623917): exceeded Critical Defect Limits for Plunger Placement at (b) (4)

(b) (4) (QR-623917): exceeded Critical Defect Limits for Plunger Placement at (b) (4)

(b) (4) (QR-623917): exceeded Critical Defect Limits for Plunger Placement at (b) (4)

No definitive root cause was identified. The investigation concluded no product impact on all (b) (4) batches filled on (b) (4) based on (b) (4) inspection followed by a passing AQL inspection. However, your firm's investigation failed to identify the deficiencies in your (b) (4) inspection program (refer to Observation 1).

C. Deviation, QR-675185, was initiated for an out of calibration result obtained for (b) (4), Stoppering Station (b) (4) (b) (4). A CAPA was implemented to shorten the preventative maintenance interval from (b) (4) to (b) (4), solely based on the limited historical

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sensor data. The root cause analysis failed to take into account the criticality of the stoppering (b) (4) in the control of the critical stoppering process for (b) (4). In addition, the standards used in the recent calibrations ((b) (4)) did not cover the full acceptable range for (b) (4) Stoppering (b) (4) for (b) (4) ((b) (4)).

D. (b) (4) Batch (b) (4) was manufactured on December 20, 2023 and released on January 23, 2024. The critical defect % for the batch was recorded as (b) (4) which exceeds the range of (b) (4). A deviation was not initiated to investigate the impact of action limit excursion on the product quality.

QUALITY SYSTEM

OBSERVATION 4

The responsibilities and procedures applicable to the quality control unit are not fully followed.

Specifically,

A. Your firm failed to exercise appropriate controls to protect the electronic data acquisition systems used for (b) (4) (b) (4) manufacturing and testing. For example, audit trails enabled in the process control and data acquisition systems are not reviewed for each data set during the batch review processes.

B. Your firm failed to ensure all meta data not directly included with the batch record, such as logbooks are reviewed prior to batch disposition.

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***DATES OF INSPECTION**

5/15/2024(Wed), 5/16/2024(Thu), 5/17/2024(Fri), 5/20/2024(Mon), 5/21/2024(Tue), 5/22/2024(Wed), 5/23/2024(Thu), 5/24/2024(Fri)

X Zhong Li
FDA Center Employee
Signed By: 2000695751
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X Melanie M Walker
Microbiologist
Signed By: Melanie M. Walker -S
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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 judgment, 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."