DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
CDER/OPQ/OPMA/Division of Biotechnology Manufacturing 10903 New Hampshire Avenue; White Oak Building 51, Room 2269 Silver Spring, MD 20993 E-mail: OPFBLAInspection483Responses@fda.hhs.gov	09/13/2023-09/21/2023
	FEI NUMBER 2000012832

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Jack Hwang, General Manager

FIRM NAME	STREET ADDRESS
PharmaEssentia Corporation	Taichung Plant No. 28 Daya Dist, 3 F; Keya West Rd., Taichung, 428
CITY, STATE, ZIP CODE, COUNTRY Taiwan	TYPE ESTABLISHMENT INSPECTED Drug Product Facility and PEG Facility

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

The visual inspection procedures are inadequate to address [redacted] (b) (4) defective filled drug product trends.

a. The visual inspection procedures lack scientific justification to support defect categories such as critical, major, and minor. For example, you have classified liquid between stopper and broken container as major defect types, although these defects may compromise the integrity of the drug product container closure and product sterility. You allow approximately three of these defects per batch without the requirement to investigate during your AQL inspections. If liquid between stopper and broken container defects were categorized as critical defects, seven out of [redacted] (b) (4) batches would exceed the critical defect limit of [redacted] (b) (4) %.

b. The visual inspection procedures do not support identifying atypical defective product trends. For example, there have been liquid between stopper in 12 out of [redacted] (b) (4) batches of [redacted] (b) (4) drug product filled [redacted] (b) (4) you manufactured and up to [redacted] (b) (4) % of the filled [redacted] (b) (4) had liquid between the stopper. Also, there have been black/white particles, fibers, glass, or other foreign particles in 12 out of [redacted] (b) (4) batches of [redacted] (b) (4) drug product filled [redacted] (b) (4) you manufactured. However, you failed to investigate these atypical defective product trends.

c. The records of manual visual inspection results lack details such as the specific cavities of the [redacted] (b) (4) containing product, the type of damage or abnormal stopper, or pictures.

d. Your manual visual inspection initial qualification is inadequate as you use the same visual inspection kit for consecutive visual inspection qualifications that are performed on the same or

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	Madushini Dharmasena Hamet Touré	Madushini Dharmasena, Ph.D., Senior Pharmaceutical Quality Assessor Hamet Touré, PharmD MPH, Regulatory Officer	09/21/2023

next day.

OBSERVATION 2

The air flow pattern testing studies did not include all operations such as setup and assembly, normal and unusual interventions, unassisted equipment operation including filling to demonstrate unidirectional airflow within the Class A classified Restricted Assess Barrier System (RABS). Therefore, your products intended to be sterile are produced in an environment that may not provide adequate protection against the risk of contamination. For example, the following operations and practices were not performed during air flow pattern testing studies:

a. Making critical aseptic connections
b. Placing (b) (4) assembly, (b) (4) sterilized secondary product contact items such as stopper lanes, stopper (b) (4) (b) (4) (b) (4) and other (b) (4) tools inside the RABS
c. Setup (b) (4) inside the RABS
d. Assembling of the (b) (4) sterilized secondary product contact items
e. Assembly of stopper (b) (4) and removing the cover
f. Actual filling of a liquid.

OBSERVATION 3

The (b) (4) drug product manufacturing process is not adequately controlled or monitored to ensure that process limits conform to specifications.

a. The position of the (b) (4) is not adequately controlled. The position of the (b) (4) is determined by the (b) (4) during the stoppering step. The qualification studies did not determine acceptable range for the (b) (4) when a (b) (4) (b) (4) (filling machine setting for stoppering parameter) is applied.
b. The (b) (4) is not controlled or monitored during sterile (b) (4) The sterile (b) (4) (b) (4) is controlled as a process parameter by (b) (4) setting. The (b) (4) (b) (4) of the sterile (b) (4) will not detect (b) (4)
c. The endotoxin limits have not been established for the formulation (b) (4) The preparation of the formulation (b) (4) involves (b) (4) (b) (4) Therefore, contaminants could be introduced during formulation (b) (4) preparation. Therefore, endotoxin excursion in formulation (b) (4) will not be detected and thus, will not prevent endotoxin entering the product stream prior to (b) (4) with the drug substance.

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OBSERVATION 4

Procedures designed to prevent microbiological contamination of [redacted] drug product purporting to be sterile are not established and followed. Specifically,

a. The [redacted] secondary product contact items such as stopper lanes, stopper [redacted] and other [redacted] tools are placed inside the RABS and outer packaging are removed or cut [redacted] prior to filling to expose these items. However, environmental monitoring is not performed during these [redacted] to assure that the exposed items are protected by the Grade A air.

b. The sterility of the [redacted] could not be assured as a [redacted] tray was placed very close to the [redacted] at the [redacted] filling to collect the [redacted] of the [redacted] and the liquid in the tray could splash from the tray. In addition, there is no assurance that the tray is sterile as there is no documentation in the batch records that the tray is [redacted] with other [redacted] items before placing in the RABS.

c. Operators did not practice aseptic techniques such as changing into a new pair of sterile gloves/sterile sleeves prior to performing the sterile connection between the sterilizing [redacted] assembly and sampling bag assembly in Grade B and sampling bag assembly in Grade B and the [redacted] inside the RABS. These sterile connections were made on a [redacted] in the Grade B area. In addition, the [redacted] was not cleaned immediately prior to performing the operations and EM samples from the [redacted] was not taken after the operations.

OBSERVATION 5

The [redacted] sterilization validation of direct and indirect sterile product-contact items is not sufficient to demonstrate sterility assurance:

a. Bioindicators (BIs) incubation conditions used during sterile drug product contact equipment [redacted] validation studies are inadequate to demonstrate that the [redacted] cycle provides a sterility assurance level of at least [redacted] and, thus, there is no assurance that the direct and indirect sterile drug product contact equipment is sterilized during [redacted] sterilization [redacted] the BIs used for the product contact [redacted] set and indirect product contact stopper bowl,

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stopper lane, stopper [redacted] during the [redacted] validation studies. An [redacted] is not sufficient to determine whether BIs spores exposed to the sterilization cycle exhibit growth.

b. The [redacted] sterilization validation of the [redacted] tray used to collect the [redacted] of the [redacted] could not be determined as there is no written record of this item in TW01-FP-RQ-007S-000002, summary report of [redacted] Re-Qualification 2023 report. In addition, sterility of this item could not be determined as there is no record of this item in the batch record.

OBSERVATION 6

The deviations and/or investigations are not always raised due to nonconformance events or incidents are not adequately investigated. For example,

a. During the manufacturing of [redacted] the operator noted on the master batch record that five [redacted] were not stoppered and removed by the operator. However, no deviation or incident report was raised to investigate the root cause for this event.
b. During the manufacturing of [redacted] the operator noted on the master batch record that five [redacted] in the [redacted] tub could not be stoppered, and these [redacted] were removed. The operator noted that this was probably due to missing [redacted] in the [redacted] tub and, thus, the [redacted] of [redacted] could not be maintained. However, no investigation was performed to investigate the root cause for the missing [redacted]
c. During the manufacturing of [redacted] the operator noted on the master batch record that five [redacted] in [redacted] tub could not be stoppered, and these [redacted] were removed. The operator noted that this was probably due to [redacted] with broken flange in the last row of the tub and, thus, the [redacted] of [redacted] could not be maintained. However, no investigation was performed to determine root cause for the broken [redacted] flange.
d. During the manufacturing of [redacted] the operator noted that [redacted] tub was rejected by the filling machine. However, no investigation was performed to determine root cause for the tub rejection.

OBSERVATION 7

Procedures to control environmental conditions have not been adequately established. Specifically,

a. The personnel monitoring limits established for operators performing operations in the [redacted] RABS are inadequate to meet acceptance criteria for Grade A (ISO 5). During the filling operation setup on September 15, 2023, the operator did not wear sterile sleeve covers and the operator's lower forearms and the upper arms moved inside the RABS when placing the stopper bowl. However, operator's right- and left-hand finger monitoring limits meet the requirements for Grade B (ISO 7). The operators right and left lower forearm are not monitored. The operator's monitoring did not occur immediately following the [redacted] intervention. Instead,

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the operator sanitized the hands and continued working in room (b) (4) personnel monitoring occurred at the end of filling.

b. The current Grade B environmental monitoring locations (b) (4) are inadequate as worst-case locations in terms of process operations were not considered.

OBSERVATION 8

Adequate procedural controls to protect the electronic data acquisition systems have not been established. Specifically,

a. Data files from Lonza equipment L-346 and L-009 for the kinetic turbidimetric LAL method are saved locally on the C drive of the computers connected to the Lonza reader. Data files are saved to the server (b) (4) at (b) (4) However, data files from the C drive can be accessed by QA and IT staff and are therefore not controlled adequately.

OBSERVATION 9

The incoming material are released for manufacturing operations prior to completing the final testing and, thus, there is no assurance that incoming material meets the specification and suitable for manufacturing. For example,

a. The stopper lots (b) (4) have been pre-released for use in filling operations prior to final testing were completed. These stopper lots were pre-released for filling operations to manufacture (b) (4) media fills, (b) (4) engineering, and (b) (4) PPQ batches and subsequently obtained full release.

b. The (b) (4) lots (b) (4) have been pre-released for use in filling operations prior to final testing was completed. These (b) (4) lots were pre-

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released for filling operations to manufacture [redacted] media fills, [redacted] engineering, [redacted] demo, and [redacted] PPQ batches and subsequently obtained full release.

APPEARS THIS WAY ON ORIGINAL