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	3/13/2024-3/22/2024*
	FEI NUMBER 3002807834

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Mr. Yasuaki Muguruma, Plant Manager

FIRM NAME	STREET ADDRESS
Second Tokushima Factory, Otsuka Pharmaceutical Co., Ltd.	224-18, Kawauchi-Cho
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Tokushima, Tokushima, 771-0182 Japan	Drug Product and Steile/Non Sterile Drug Substance 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 OBSERVED:

OBSERVATION 1

Equipment and utensils are not cleaned, maintained and sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically,

The non-dedicated (b) (4) Equipment ID# 5G2-EQ12, Model (b) (4) is not adequately cleaned at appropriate intervals to prevent cross-contamination from drug substances previously manufactured. On 03/18/2024, after the completion of a production campaign of (b) (4) lots of (b) (4) (b) (4) (Lot # (b) (4) visible whitish residue found on the (b) (4) duct after the (b) (4) (b) (4) filter. A swab sample collected on 3/18/2024 for chemical analysis by HPLC to identify the presence of drug substances of previously manufactured drug products showed unknown peaks and presence of (b) (4) drug substance manufactured from 03/05/2024 through 03/08/2024.

OBSERVATION 2

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

Specifically,

SEE REVERSE OF THIS PAGE

EMPLOYEE(S) SIGNATURE

Patty P Kaewussdangkul, Investigator

X Patty P Kaewussdangkul Investigator Signed By: Patty P. Kaewussdangkul -S Date Signed: 03-22-2024 14:48:34

DATE ISSUED

3/22/2024

a) Your firm dynamic smoke studies are inadequate because they do not fully simulate/mimic routine production to verify that operators and equipment do not alter, impede or obstruct unidirectional air flow from the HEPA filters where your sterile active pharmaceutical ingredient, [redacted] is filled into [redacted] sterile bags [redacted] For example, your most recent dynamic smoke studies demonstrated the filling process of [redacted] product which is not representative of routine operations. In addition, no dynamic smoke studies were performed to capture the staging of equipment, set up and replacement of [redacted] plates or the packaging process.

b) Your firm has [redacted] fixed particle counters in your dedicated [redacted] dedicated used to fill and package sterile grade [redacted] API. [redacted] During review of smoke studies and visual observation of the filling and packaging operations of sterile [redacted] API, Lot # [redacted] Exp. [redacted] on 3/20/2024, the particle probe is oriented towards first air and away from production which is not meaningful to monitor and ensure the cleanliness of the Grade A environment during production. Sterile grade [redacted] API is further processed by [redacted] into sterile finished drug products that are distributed in the United States.

OBSERVATION 3
Deviations from written sampling plans are not justified.

Specifically,

Your document entitled, "Specification for Environment Control", Specification no. SHC-17, Effective September 26, 2023 states to "perform contact plate bacteria sampling at a total of [redacted] locations". On 3/20/2024, I observed the firm conduct [redacted] sampling of [redacted] pre-determined locations in the

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Grade A (b) (4) using (b) (4) contact plates (b) (4) of the filling and packaging production process of sterile grade, (b) (4) API, Lot # (b) (4) Exp. (b) (4) No scientific justification was provided to explain the practice or adequacy of using one contact plate to sample two separate locations in the Grade A environment.

OBSERVATION 4

Reports of analysis from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications, without performing at least one specific identity test on each component.

Specifically,

a) Your firm routinely purchases (b) (4) a product contact raw material used in the production process of sterile grade (b) (4) active pharmaceutical ingredient (API). Your firm maintains the certificate of analyses provided from your suppliers but failed to perform the identity test on at least (b) (4) lots received since 03/1/2022. Sterile grade (b) (4) API is distributed to finished product manufacturing facilities to be made into US products.

a) Your firm routinely purchases (b) (4) from your suppliers used in the production of your active pharmaceutical ingredients however, your firm does not test these products for (b) (4) contamination. For example,

- (b) (4) lots of (b) (4) received since March 1, 2022 was not tested for (b) (4) contamination but used in the production of non-sterile and sterile grade (b) (4) API.
- (b) (4) lots of (b) (4) received since March 1, 2022 was not tested for

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[redacted] (b) (4) contamination but used in the manufacturing of [redacted] (b) (4) API.

OBSERVATION 5

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

Specifically,

Your firm received a complaint from your 3rd party contract testing laboratory responsible for storing and testing your firm's stability samples. During the 24-month stability test for [redacted] (b) (4) mg tablets, Lot [redacted] (b) (4) the contract laboratory found "non-representative" results during the appearance test, a finished product release specification. Your firm failed to fully investigate the complaint and determined the root cause to be inconclusive without due diligence to identify the nature of the smudge such as sending to a laboratory that has the capability to conduct further testing.

***DATES OF INSPECTION**

3/13/2024(Wed), 3/14/2024(Thu), 3/15/2024(Fri), 3/18/2024(Mon), 3/19/2024(Tue), 3/20/2024(Wed), 3/21/2024(Thu), 3/22/2024(Fri)

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