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	2/3/2025-2/14/2025*
	FEI NUMBER 3008565058

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Umesh Gupta, Senior VP & Site Head

FIRM NAME	STREET ADDRESS
Glenmark Pharmaceuticals Ltd	Plot No 2, Phase - II, Pharma Zone, SEZ
CITY, STATE, ZIP CODE, COUNTRY Pithampur, Madhya Pradesh, 454774 India	TYPE ESTABLISHMENT INSPECTED 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

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

Specifically, you failed to implement adequate contamination control procedures to ensure drug products manufactured at your site using non-dedicated equipment are not cross-contaminated by the residues from the [redacted] (b) (4) drug product [redacted] (b) (4) For example:

A. Since [redacted] (b) (4) there were approximately [redacted] (b) (4) incidents of detected [redacted] (b) (4) carryover residue after cleaning of non-dedicated major production equipment. In three of these [redacted] (b) (4) incidents, the detected residue level exceeded the [redacted] (b) (4) ppm specification indicating that the current cleaning processes are not able to consistently remove [redacted] (b) (4) cross contamination although the three resulting impacted batches were rejected later on. This equipment was also used to manufacture [redacted] (b) (4) drug products, including [redacted] (b) (4) impacted batches that were shipped into the US as shown below.

[redacted] (b) (4)

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B. Cleaning validation studies performed for [redacted] Tablets (validation report: CAMVR/P/18/03-02, effective date: October 24, 2018, LOD: [redacted] ppm, LOQ: [redacted] ppm) are inadequate. During these studies, while establishing a minimum acceptable residue carryover, you failed to consider unique nature of these drugs [redacted] and potential contamination risk to other products manufactured using shared equipment. For example:

a. From [redacted] to [redacted] No routine monitoring of [redacted] residue was performed during product change over cleaning and/or [redacted] periodic cleaning verification. Some examples of [redacted] products produced on this shared equipment before [redacted] and shipped to the US that are still within expiry. For example, between, from [redacted] to [redacted] the site shipped approximately [redacted] impacted batches (batches of [redacted] products, [redacted] bottles) to the US.

b. From [redacted] to current: you started monitoring of [redacted] residue after product change over cleaning at [redacted] ppm level for [redacted] Tablets. From [redacted] to 01/2025, the site shipped approximately [redacted] batches of [redacted] products, [redacted] bottles (live as of 02/14/2025) to the US.

C. The firm's VP Quality stated on 2/13/2025 that the site does not use any [redacted] decontamination agent in the facilities used in the processing of [redacted] drug products. He confirmed major production equipment used to manufacture [redacted] products is not decontaminated before it is used to manufacture [redacted] drug products.

D. The firm's control procedure CM/PD121, "Entry and Exit Procedure into the Production Facility" allows operators working in (b) (4) processing areas to work in (b) (4) processing areas the same day by following gowning and de-gowning procedures.

E. The site does not periodically test (b) (4) products manufacturing using shared equipment/facilities to ensure these products do not contain traces of (b) (4) residue.

F. The firm uses about (b) (4) dust collectors in various (b) (4) processing areas including (b) (4) equipment, (b) (4) and bulk packing etc. The dust collector filters (for re-circulated air) in these areas are not product specific. Instead, the same filter is used for all other (b) (4) products. The site does not test these filters for traces of (b) (4) residue.

G. You received two consumer complaints MC/1111/2023/0054 and MC/1111/2024/0178 on 10/18/2023 and 12/14/2024 respectively in which patients reported reaction and/or adverse drug event while using (b) (4) tablets (b) (4) mg. You manufacture (b) (4) tablets using shared facilities, equipment, and air supply that is used for (b) (4) products (b) (4) (b) (4) tablets). Your investigations for both complaints were inadequate as you failed to assess potential (b) (4) that may occur when (b) (4) drugs are manufactured using shared facilities and equipment.

OBSERVATION 2

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Separate or defined areas to prevent contamination or mix-ups are deficient regarding the manufacturing and processing operations.

Specifically, separate, or defined areas to prevent contamination are deficient regarding manufacturing of (b) (4) drug products including (b) (4) (b) (4) Tablets at your facility. For example:

A. You failed to ensure sampling, dispensing, (b) (4) and packaging operations for (b) (4) drug products (b) (4) (b) (4) Tablets) are carried out using dedicated facilities, equipment, and air supply systems. For example:

1. Sampling and dispensing areas, equipment, and air handling systems used for (b) (4) (b) (4) drug products are shared with approximately (b) (4) other routine (b) (4) US drug product configurations. After sampling and dispensing of (b) (4) drug products, you use these areas to sample & dispense other (b) (4) (b) (4) drug products without any verification by appropriate testing that these areas, equipment, and air is free from residues of (b) (4) drug products.

2. (b) (4) areas, major production equipment, and air handling systems used for (b) (4) drug products are shared with approximately (b) (4) other routine (b) (4) US drug product configurations. After (b) (4) (b) (4) of (b) (4) drug products, you use these areas for other (b) (4) drug products without any verification by appropriate testing that these areas and air is free from residues of (b) (4) drug products.

3. Primary packing areas, equipment, and air handling systems used for (b) (4) (b) (4) drug products are shared with approximately (b) (4) other routine (b) (4) (b) (4) US drug product configurations. After packing of (b) (4) drug products, you

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use these areas for other [(b) (4)] drug products without any verification by appropriate testing that these areas and air is free from residues of [(b) (4)] drug products.

B. You don't have cross-contamination prevention and control plan for routine sampling & monitoring of facilities, personnel, air supply, and equipment at appropriate intervals to demonstrate routine drug products, manufactured at the site using shared facilities, equipment, and air handling systems are not being contaminated with the traces of [(b) (4)] drug products. Your risk assessment (RA/1111/2023/0029, rev: 00) approved on 7/24/2023 is inadequate as it does not include such controls.

OBSERVATION 3

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically,

A. Multiple Out of Specification (OOS) and Out of Trend (OOT) results have been obtained for [(b) (4)] Capsules, USP for dissolution test since 2022. No specific root causes were identified; however, by statistical evaluation you have attributed these failures to the previously validated [(b) (4)] equipment critical process parameters variation at the [(b) (4)] stage. Though the annual stability batch in 2023 (batch# [(b) (4)] gave OOS results at various stability time points, as part of the impact assessment, you have tested only reserve samples from [(b) (4)] of the remaining [(b) (4)] batches that were in the market at the time of finding. All [(b) (4)] batches were manufactured using the validated [(b) (4)] process. Of the [(b) (4)] batches tested you received an additional OOS (OOS/I111/2024/0056, Batch# [(b) (4)] and the

batch was recalled. The remaining (b) (4) untested batches do not have adequate supporting stability data. Since then, your firm has released (b) (4) more batches of this product to the US market without re-validating the (b) (4) equipment critical process parameters to overcome to suspected root cause.

B. The root causes assigned to the following OOS investigations for (b) (4) Capsules USP, arising from dissolution failures were not adequately supported with evidence and/or failed to explain all the data. The specific (b) (4) types and the number used during sample preparation were not documented but an after-failure interview was used to arrive at the root cause conclusion of analyst error with the use of (b) (4) These OOS results were invalidated and retested with new samples to obtain passing results. The batches were ultimately released to the US market.

-OOS/I104/2024/0045: This investigation was opened on 9/16/2024, when dissolution testing for (b) (4) Capsules USP (b) (4) mg (Batch# (b) (4) by HPLC resulted in OOS results during release test.

-OOS/I104/2024/0059: This investigation was opened on 11/14/2024, when dissolution testing for (b) (4) Capsules USP (b) (4) mg (Batch# (b) (4) by HPLC resulted in OOS results during release test.

-OOS/I104/2024/0060: This investigation was opened on 11/16/2024, when dissolution testing for (b) (4) Capsules USP (b) (4) mg (Batch# (b) (4) by HPLC resulted in OOS results during 9M stability test.

The above three initial OOS results on dissolution test for (b) (4) Capsules USP were obtained by three different analysts on different days. The root cause identified as the improper (b) (4) and the use of specific type of (b) (4) by the analyst did not adequately explain how the passing results were obtained with remainder of the capsules in the same sample sets.

C. Your firm has recorded 8 OOS investigations for [redacted] (b) (4) Capsules since April 2024. All of them were for dissolution test and were found to be valid OOS results. The root causes identified could not be adequately supported as the failure continued until the production was terminated on [redacted] (b) (4) For example, OOS investigation, OOS/I111/2024/0062, attributed the probable root cause to the [redacted] (b) (4) of the particle size of the API, however, it would not explain how the product did not have any dissolution issues during the prior three years when approximately [redacted] (b) (4) batches were made, as there was no recent change in API source or specification. On 20 Jan 2025 you have added an addendum to your OOS investigations with a new root cause potentially arising from changes you made with the process.

D. Approximately 75 instances of extraneous peaks have been recorded during dissolution, assay, content uniformity and impurities tests by HPLC resulting from potential contaminations since 2023. Sources of contaminations have not always been identified or have root causes been adequately supported. The root causes of the extraneous peaks have been categorized as 'instrument error' (23 times), 'human error' (6 times), 'other(s)' (42 times) and remaining four are under investigation.

OBSERVATION 4

The accuracy, sensitivity, specificity and reproducibility of test methods have not been established and documented.

Specifically,

Commercial drug products and Active Pharmaceutical Ingredients (API) test methods, including in-house and compendial test methods were not validated or verified appropriately. More than [redacted] (b) (4) products and APIs are routinely released by testing with analytical test methods that have not been adequately

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validated or verified. The test methods include (b) (4) method for (b) (4) content, specific optical rotation, identification test by IR, UV and TLC. Appropriate parameters like specificity or precision have not been validated or verified. The drug products have (b) (4) and drug product batches were distributed to customers in the US and are currently in the market. The list includes, but is not limited to, the following:

(b) (4)

[redacted]

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OBSERVATION 5

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The quality control unit lacks responsibility to approve all procedures or specifications impacting on the quality of drug products.

Specifically,

Since 01 Jan 2023, approximately (b) (4) US commercial samples for stability studies have not been completed in a timely manner. These testing delays varied between 1-12 months at different stability stations as shown below:

(b) (4)

[redacted]

This delay is potentially causing several commercial batches of drug products to be in the market without having concurrently supporting stability data.

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*DATES OF INSPECTION

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