WARNING LETTER

Glenmark Pharmaceuticals Limited

MARCS-CMS 582701 — OCTOBER 03, 2019

Delivery Method:

VIA UPS

Reference #:

320-20-01

Product:

Drugs

Recipient:

Glenn Saldanha

Chairman & Managing Director

Glenmark Pharmaceuticals Limited

Glenmark House B, HDO-Corporate Building, Wing-A, B.D. Sawant Marg, Chakala, Andheri, (E)
Mumbai 400099
India

Issuing Office:

Center for Drug Evaluation and Research

10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

Dear Mr. Saldanha:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Glenmark Pharmaceuticals Limited, FEI 3005757050, at Village Kishanpura, Baddi Nalagarh Road, Baddi Solan, Himachal Pradesh, from April 15 to 20, 2019.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your May 10, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific violations including, but not limited to, the following.

Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether the batch has already been distributed (21 CFR 211.192).

Your firm failed to ensure your investigations identify appropriate root causes and you failed to implement sustainable corrective action and preventive action (CAPA).

a. You failed to thoroughly investigate multiple complaints of grittiness for your topical **(b)(4)** cream USP, **(b)(4)**%. Since November 2017, you rejected 20 batches and received at least 38 complaints about product grittiness. Product grittiness has been an ongoing formulation issue since 2010 and was a deficiency cited in the previous inspection of your facility. You proposed specific remediation for this formulation issue in your response at that time. In your response to the most recent inspection, you stated that the product grittiness issue was remediated during product reformulation in November 2018. Your response is inadequate. You did not provide sufficient data to demonstrate the robustness of the new formulation.

We acknowledge that in July 2019 you recalled all batches within expiry that were manufactured using the original formulation. However, your reformulation and market actions were not performed in a timely manner.

b. You failed to adequately investigate multiple temperature excursions that occurred during shipping of your drug products. Your investigations into the temperature excursions did not include timely actions to prevent their recurrence.

For example, in May 2018, **(b)(4)** cream USP, **(b)(4)**% batches were exposed to temperature excursions up to **(b)(4)**°C and **(b)(4)**°C for **(b)(4)** while in transit to the United States. **(b)(4)** cream should be stored between **(b)(4)**°C. In July 2018, a **(b)(4)**USP, **(b)(4)**% batch was exposed to **(b)(4)**°C for **(b)(4)** while in transit to the United States. **(b)(4)** should be stored between **(b)(4)**°C. These **(b)(4)** batches were distributed to the U.S.

Inadequate investigation into temperature excursions is an ongoing issue and was a deficiency cited during the previous inspection of your facility. Notably, you performed a study to determine the impact of elevated temperature on **(b)(4)** cream USP, **(b)(4)**%. The study showed phase separation of the product at **(b)(4)**°C.

In your response, you stated that you will perform an additional temperature excursion study as well as conduct a long-term stability study. You also stated that you will investigate all confirmed out-of-specification (OOS) results during the temperature excursion studies and will notify the FDA, as appropriate.

Your response is inadequate. You did not provide an adequate risk assessment for marketed batches exposed to temperatures outside the labeled storage conditions. Also, your response mentioned the implementation of new shipping practices to protect your products from thermal excursions, but they were not implemented in a timely manner.

c. You failed to adequately investigate multiple OOS test results for critical product attributes, such as **(b)(4)** For example, in April 2018, **(b)(4)** batch **(b)(4)** failed **(b)(4)** Additionally, in February 2019, **(b)(4)** ointment USP **(b)(4)**% batch **(b)(4)** failed **(b)(4)** These batches were ultimately rejected. However, your investigations into these failures did not determine an appropriate root cause and ensure effective CAPA.

In your response, you indicated that you plan to hire a consultant to enhance the quality of your investigations. Your response is inadequate. You did not assess the potential impact to product quality and the failure to identify potential root causes.

d. You failed to adequately investigate more than 70 consumer complaints associated with punctures, cracks, and holes in **(b)(4)** for various drug products including, but not limited to, **(b)(4)** ointment USP, **(b)(4)**%, **(b)(4)** cream USP, and **(b)(4)** ointment USP, **(b)(4)**%. Your investigations failed to adequately address the scope and cause of these serious container/closure system defects and evaluate other drug products that have similar manufacturing quality signals such as complaints, or that use the same supplier.

In your response, you stated that the root cause for the complaints was improper "handling by folding and refolding of the **(b)(4)**" by consumers. In addition, you stated that because the complaint rate is insignificant, there is no risk to marketed batches. However, you closed more than 50 of the complaints, without CAPA to prevent recurrence of similar quality defects.

Your quality system for investigations is inadequate and does not ensure consistent production of safe and effective products. Your firm has repeatedly failed to determine the root cause and implement CAPA to prevent the recurrence of these serious product quality defects.

In response to this letter, provide the following:

• A comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, OOS results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, CAPA effectiveness, quality unit oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.

• An independent assessment and remediation plan for your CAPA program. Summarize how your firm will effectively conduct root cause analysis, assure CAPA effectiveness, regularly review investigation trends, enhance staff competencies, implement improvement to the CAPA program when needed, ensure appropriate quality unit decision rights, and is fully supported by executive management.

• A detailed review of the robustness of the new formulation for **(b)(4)** cream USP, **(b)(4)**%, including but not limited to all manufacturing and quality data (e.g., complaints, OOS, deviations, rejects, stability, data to fully assess whether the new formulation is robust or not).

• A comprehensive, independent review of your material system to determine whether all suppliers of components, containers, and closures, are each qualified and the materials are assigned appropriate expiration or retest dates. The review should also determine whether incoming material controls are adequate to prevent use of unsuitable components, containers, and closures.

• Independent review of all your processes to determine their state of control. Also, provide your detailed program for designing, validating, maintaining, controlling and monitoring each of your manufacturing processes that includes vigilant monitoring of intra-batch and inter-batch variation to ensure an ongoing state

of control. Also include your qualification program for your equipment and facility.

Conclusion

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov (mailto:drugshortages@fda.hhs.gov), so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations may also result in the FDA refusing admission of articles manufactured at Glenmark Pharmaceuticals Limited, at Village Kishanpura, Baddi Nalagarh Road, Baddi Solan, Himachal Pradesh, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov) or mail your reply to:

Deyaa Shaheen
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4235
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3005757050.

Sincerely,
/S/
/Francis Godwin/

Francis Godwin
Director

Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

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