WARNING LETTER

Lupin Limited

MARCS-CMS 633703 — SEPTEMBER 27, 2022

Delivery Method:

Via Email

Product:

Drugs

Recipient:

Mr. Akash Patel

Site Head and Senior General Manager Manufacturing

Lupin Limited

T-142, MIDC Tarapur via Boisar
Palghar 401506 Maharashtra
India

Issuing Office:

Center for Drug Evaluation and Research | CDER

United States

Warning Letter 320-22-25

September 27, 2022

Dear Mr. Patel:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Lupin Limited, FEI 3002807512, at T-142, MIDC Tarapur via Boisar, Palghar, from March 22 to April 4, 2022.

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API 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 April 25, 2022, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operations into compliance with CGMP.

During our inspection, our investigator observed specific deviations including, but not limited to, the following.

1. Failure to establish adequate written procedures for cleaning equipment and its release for use in manufacture of intermediates and API.

Your firm performed multiple risk assessments with the purpose to verify whether existing cleaning procedures and practices eliminate or reduce genotoxic impurities, including **(b)(4)** and **(b)(4)** impurities, generated through the manufacture of **(b)(4)** drugs, after you detected **(b)(4)** impurities in your API. You also performed risk assessments to evaluate whether existing cleaning procedures reduce cross-contamination of intermediates and API by evaluating residues on non-dedicated production equipment and within recovered solvents. Your risk assessments lacked data to support that existing equipment cleaning procedures are effective in removing **(b)(4)** along with residual API from each respective piece of equipment to acceptable levels.

For example, your hypothesis testing protocol to assess the potential for cross-contamination derived from non-dedicated equipment in the **(b)(4)** and **(b)(4)** buildings following the manufacture of **(b)(4)** API and Type A (product-to-product changeover) cleaning of equipment is deficient in that:

- The two executed protocols identify **(b)(4)** batches of **(b)(4)** API manufactured on non-dedicated equipment following the manufacture of **(b)(4)** API from 2019-2021. Quantifiable levels of **(b)(4)** (**(b)(4)**) (**(b)(4)** ppm) near the limit of not more than **(b)(4)** ppm was identified in four of the **(b)(4)** batches. No further investigation into these findings was conducted.
- You lacked documentation to support your identification of the first batch of **(b)(4)**, **(b)(4)** or **(b)(4)** APIs manufactured on non-dedicated equipment following changeover from **(b)(4)** API manufacture. Specific pieces of equipment used to manufacture these products are not identified. You lacked documentation demonstrating these initial post-changeover batches were manufactured on or with the same equipment as the preceding **(b)(4)** API.
- The protocol does not address cross-contamination from indirect sources including non-dedicated equipment used to recover solvents.

The identification of genotoxic impurities in quantities near their established limits suggests excursions are possible. All intermediates and API manufactured on non-dedicated equipment used to manufacture **(b)(4)** drugs should be subject to validated sampling and analytical testing to ensure they are not contaminated with unacceptable levels of genotoxic impurities.

You provided conflicting data with respect to the detection and quantitation of genotoxic impurities in **(b)(4)** API following changeover from **(b)(4)** API manufacture. For example, you reported quantifiable levels of **(b)(4)** impurities **(b)(4)**, **(b)(4)**, and/or **(b)(4)** in all **(b)(4)** batches of **(b)(4)** API tested during your study investigating potential cumulative carryover of genotoxic residues following changeover from **(b)(4)** API manufacture. However, your quality risk assessment stated the same **(b)(4)** impurities were not detected in the same product and batches. You disregarded the unfavorable analytical results without appropriate scientific justification. You concluded there was no risk of carryover of these genotoxic impurities to other intermediates and API manufactured with non-dedicated equipment.

In your response, you committed to restrict the manufacture of **(b)(4)** and **(b)(4)** API to dedicated equipment and to use a dedicated solvent recovery unit. However, you committed to only dedicate solvent recovery tanks during the manufacturing campaigns of specific products. As your solvent recovery tanks are not dedicated to specific products only, the cross-contamination risks remain and you must appropriately assess the risk and validate procedures to ensure cross-contamination does not occur from your non-dedicated solvent recovery equipment.

In response to this letter, provide:

• A comprehensive, independent retrospective assessment of your cleaning effectiveness to evaluate the scope of cross-contamination hazards. Include the identity of residues, other manufacturing equipment that may have been improperly cleaned, and an assessment whether cross-contaminated products may have been released for distribution. The assessment should identify any inadequacies of cleaning procedures and practices, and encompass each piece of manufacturing equipment used to manufacture more than one product, including both API and finished products.

• A corrective action and preventive action plan, based on the retrospective assessment of your cleaning program, that includes appropriate remediations to your cleaning processes and practices, and timelines for completion. Provide a detailed summary of vulnerabilities in your process for lifecycle management of equipment cleaning. Describe improvements to your cleaning program, including enhancements to cleaning effectiveness; improved ongoing verification of proper cleaning execution for all products and equipment; and all other needed remediations.

• Appropriate improvements to your cleaning validation program, with special emphasis on incorporating conditions identified as worst case in your drug manufacturing operation. This should include but not be limited to identification and evaluation of all worst-case:
  o drugs with higher toxicities
  o drugs with higher drug potencies
  o drugs of lower solubility in their cleaning solvents
  o drugs with characteristics that make them difficult to clean
  o swabbing locations for areas that are most difficult to clean
  o maximum hold times before cleaning
  o In addition, describe the steps that must be taken in your change management system before introduction of new manufacturing equipment or a new product.
  o A summary of updated standard operating procedures (SOPs) that ensure an appropriate program is in place for verification and validation of cleaning procedures for products, processes, and equipment.

2. Failure to establish written procedures to monitor the progress and control the performance of processing steps that may cause variability in the quality characteristics of your intermediates and API.

Your **(b)(4)** process for the manufacture of the API **(b)(4)** and **(b)(4)** results in quantifiable levels of **(b)(4)** Impurity **(b)(4)** at an irregular frequency. For example, you sampled and performed analytical testing to detect and quantify levels of **(b)(4)** and **(b)(4)** impurity levels in **(b)(4)** batches of **(b)(4)** and **(b)(4)** batches of **(b)(4)** APIs manufactured via the **(b)(4)** process. One batch each of **(b)(4)** (**(b)(4)** ppm against a limit of **(b)(4)** ppm) and **(b)(4)** (**(b)(4)** ppm against a limit of not more than **(b)(4)** ppm) yielded quantifiable levels of **(b)(4)** Impurity **(b)(4)**.

You also performed a series of benchtop and commercial scale studies to assess the efficacy of processing steps that theoretically reduce the level of genotoxic impurities including **(b)(4)** Impurity **(b)(4)**. These studies concluded all the **(b)(4)** impurities are purged out effectively and there was no additional need for in-process monitoring of **(b)(4)** and **(b)(4)** impurities. This is despite the aforementioned analytical results derived from commercialized batches of API. You did not further investigate the appearance of quantifiable levels of **(b)(4)** Impurity **(b)(4)** in some batches of **(b)(4)** and **(b)(4)** even though you declare the manufacturing process capable of effectively purging this impurity.

While your benchtop data suggests your purging is effective, your commercial manufacturing data shows your purging does not remove all genotoxic impurities to a consistent level. Given the variability found in impurities levels in API which may stem from special cause variation, you will need to either:

• Add a test for **(b)(4)** Impurity **(b)(4)** or its precursors upstream with spike/purge data to show **(b)(4)** Impurity **(b)(4)** is <**(b)(4)**% of the allowable limit in the drug substance

• Or add a test for **(b)(4)** Impurity **(b)(4)** to the drug substance specification

Confirmation of your improved process should be done by collecting additional data to support batch release, such as batch release testing for **(b)(4)** impurities.

We acknowledge your commitments to performing a process capability analysis and to perform a comprehensive risk-based review for currently manufactured products.

In response to this letter, provide:

• Your investigation, including corrective actions and preventive actions and the dates of their planned implementation, the formation, monitoring, and control of genotoxic impurities in intermediates and APIs manufactured by your firm.

• The data and conclusions from your process capability analysis for the reduction or removal of genotoxic impurities during the manufacture of **(b)(4)** and **(b)(4)** APIs. Your analysis should also discuss the analysis of special cause variation and what controls you will put into place to ensure drug quality.

• The procedure for your risk-based review for all currently manufactured products.

3. Failure to investigate all critical deviations.

You failed to identify and investigate all critical deviations including limit excursions. For example, you obtained an out-of-specification (OOS) result of **(b)(4)** ppm against a limit of not more than **(b)(4)** ppm during execution of a cleaning verification protocol for **(b)(4)**. The final report records the OOS swab sample as being taken from a **(b)(4)** following the manufacture of batch **(b)(4)** and completing a Type B cleaning. Section 10.0 of the final report notes no deviations or OOS results were observed despite the OOS result. The report concludes the Type B cleaning of equipment is validated to effectively remove chemical residues from equipment despite failing data and the subsequent review and approval of this report.

In response to this letter, provide:

• A comprehensive assessment and remediation plan to ensure your quality unit (QU) is given the authority and resources to effectively function. The assessment should also include, but not be limited to:
  o A determination of whether procedures used by your firm are robust and appropriate
  o Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices
  o A complete and final review of each batch and its related information before the QU disposition decision
  o Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products.

• A retrospective review of all data used to qualify or validate processes associated with the manufacture of APIs within expiry or release materials within expiry to identify all instances of non-conforming results and ensure they are addressed appropriately.

Drug Production Suspended

We acknowledge your commitment to suspend production of drugs for the U.S. market. In response to this letter, clarify whether you intend to resume manufacturing any drugs at this facility in the future.

If you plan to resume manufacturing drugs for the U.S. market, notify this office before resuming your operations.

Conclusion

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

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, 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). This also 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.

Correct any deviations promptly. FDA may withhold approval of new applications or supplements listing your firm as a drug manufacturer until any deviations are completely addressed and we confirm your compliance with CGMP. We may re-inspect to verify that you have completed corrective actions to any deviations.

Failure to address any deviations may also result in the FDA refusing admission of articles manufactured at Lupin Limited, at T-142, MIDC Tarapur via Boisar, Palghar, 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 that appear to be adulterated may be detained or refused 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).

This letter notifies you of our findings and provides you an opportunity to address the above deficiencies. After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done to address any deviations and to prevent their recurrence. In response to this letter, you may provide additional information for our consideration as we continue to assess your activities and practices. 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. Identify your response with FEI 3002807512 and ATTN: Jason F. Chancey.

Sincerely,
/S/

Francis Godwin
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

Cc: Mr. Nilesh Gupta, Managing Director

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