Lupin Limited 11/6/17

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS **Warning Letter 320-18-06**

November 6, 2017

Mr. Nilesh Gupta
Managing Director
Lupin Limited
B/4 Laxmi Towers,
Bandra Kurla Complex, Bandra (E)
Mumbai 400 051
India

Dear Mr. Gupta:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facilities: Lupin Limited at 15-B, Phase 1A, Verna Industrial Area, Verna, Salcette, Goa from March 27 to April 7, 2017 ("Lupin Goa") and Lupin Limited at Unit 2–Plot No. 2, SEZ Phase-II, Misc., Apparel Park, District Dhar, Pithampur, Indore, Madhya Pradesh, from May 8 to May 19, 2017 ("Lupin Indore").

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 April 28, 2017, response for Lupin Goa, and June 7, 2017, response for Lupin Indore in detail and acknowledge receipt of your subsequent correspondence.

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

Lupin Goa

1. 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 or not the batch has already been distributed (21 CFR 211.192).

Your firm frequently invalidated initial out-of-specification (OOS) laboratory results without an adequate investigation that addressed potential manufacturing causes.

A. Assay Failure

While conducting component release testing on **(b)(4)** active pharmaceutical ingredient (API) batch **(b)(4)**, your firm obtained a failing assay result of **(b)(4)**% (specification **(b)(4)**% to **(b)(4)**%).

Data from the investigation demonstrated that multiple retest results were comparable to the initial OOS result. Initial retests yielded four results ranging from **(b)(4)**% to **(b)(4)**%. These results included a freshly prepared sample, which tested at **(b)(4)**%.

A second analyst tested a new set of samples and obtained results including **(b)(4)**%, **(b)(4)**%, and **(b)(4)**%. You then performed the test again. Only the last samples yielded significantly different assay results (**(b)(4)**–**(b)(4)**%).

Despite the findings of multiple values close to the original OOS value, your firm invalidated the initial failing result, stating that the initial result "shall be considered an outlier and retest results shall be reported as final results." Although the investigation failed to identify a conclusive laboratory root cause, you did not conduct an evaluation of your supplier, and reported an average result for batch release.

It is not appropriate to use an "outlier test" to invalidate your API assay result. Such statistical treatments do not identify the cause of an extreme observation, and are only of informational use in an investigation of chemical testing. Further, in this case, your investigation included multiple retests that were the same or very similar to the original OOS result.

Our inspection also revealed additional inappropriate uses of outlier testing. Your firm released other raw materials and drug product batches by retesting and concluding that the original OOS result was an "outlier."

We acknowledge your firm's change control on January 18, 2017, to remove the outlier test in your *Handling of Out of Specification Test Results* standard operating procedure (SOP). You also reversed your original decision to release **(b)(4)** batch **(b)(4)**, and have now rejected it. However, your response did not address API quality issues that may have caused the low assay, and lacked an adequate reassessment of the other batches released with the outlier test.

B. Content Uniformity Failure

Your investigation of content uniformity OOS results for **(b)(4)** mg tablets for batch **(b)(4)** was inadequate. Two individual units and the acceptance value (AV) were OOS for this batch, which was an exhibit batch filed in your **(b)(4)**.

The initial assessment of the OOS results found no evidence of laboratory error by the analyst. Retests from stock solution and re-sonicated samples yielded results consistent with the original OOS results, and ruled out improper sonication and dilution error as root causes. Although the investigation did not demonstrate a conclusive assignable cause, you surmised that the "probable laboratory error" was inadequate cleaning of the **(b)(4)** shaft by the analyst. You then invalidated the initial OOS results and reported test results from a new set of **(b)(4)** units that passed specifications. Your firm's investigation indicated that this "confirmed" that there was a laboratory error.

When an investigation lacks conclusive evidence of laboratory error, a thorough investigation of potential manufacturing causes must be performed. The test of **(b)(4)** units for content uniformity is intended to represent different parts of a batch, and to help detect if portions of the batch are non-uniform. Your acceptance of the results from testing a new set of **(b)(4)** units based on an unproven hypothesis was insufficient to conclude the investigation. In addition to further laboratory investigation, your firm should have identified possible manufacturing causes and more extensively characterized uniformity of the batch.

Insufficient cleaning of the **(b)(4)** shaft was also cited in a previous investigation as the presumed root cause of OOS content uniformity results for batch **(b)(4)** of **(b)(4)** mg tablets. A different analyst performed that test, and your corrective action and preventive action (CAPA) plan required retraining staff.

In your response, you indicate that SOP CQA-063 *Analyst Qualification* has been revised to state that "if **(b)(4)** times error is repeated then the analyst shall be requalified on the specific analytical technique." However, your response did not sufficiently address improvements in your quality system that will ensure that flaws in written laboratory procedures and analytical equipment will be corrected.

In response to this letter, provide an independent assessment of Lupin Goa, including:

- All invalidated OOS (in-process and finished testing) results obtained for products on the U.S. market. Assess whether the scientific justification and evidence was conclusive. For investigations that conclusively established laboratory root cause, determine adequacy of the CAPA, and ensure the other laboratory methods that are vulnerable to the same root cause have been identified for remediation. For any OOS that had an inconclusive or no root cause identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of manufacturing steps, process capability, deviation history, batch failure history). Provide a CAPA plan that identifies the potential manufacturing root causes for each such investigation, and includes process improvements where appropriate.
- Historical performance of all laboratory methods. Assess adequacy of instructions for each method, suitability of laboratory equipment, and competency of analysts. Determine errors that have occurred on multiple occasions over the history of the method, and identify further CAPA measures needed to enhance robustness.
- Your overall system for investigating OOS results. Provide a CAPA to improve quality of OOS investigations in all Lupin facilities. Elements of your CAPA should include, but not be limited to, enhanced quality assurance participation in individual laboratory investigations and in identifying adverse laboratory control trends.

Also provide your updated laboratory investigation procedure. Describe how your revised procedure ensures that all OOS investigations will extend to a full review of potential manufacturing root causes whenever a cause is not conclusively found in the laboratory.

For more information about handling OOS results and conducting appropriate investigations, see FDA's guidance document, *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*, at **https://www.fda.gov/downloads/drugs/guidances/ucm070287.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm070287.pdf)**.

2. Your firm failed to establish appropriate time limits for the completion of each phase of production to assure the quality of the drug product (21 CFR 211.111).

Bulk **(b)(4)** used in solid **(b)(4)** dosage form manufacturing were held for excessive periods during commercial batch manufacturing without adequate hold time studies or scientific justification. For example, in many instances, bulk **(b)(4)** for multiple drug products were held for longer than **(b)(4)**, including some held significantly beyond **(b)(4)**. Despite these excessive **(b)(4)** hold times, you released the **(b)(4)** for **(b)(4)**, and rarely placed the finished product batches in your stability program.

Studies intended to support these inordinate **(b)(4)** hold times were inadequate because the holding conditions were not representative of the actual operation. While your *Hold Time Study* SOP states that the quantity studied "shall be representative of Complete Batch," your studies routinely used only **(b)(4)** of the **(b)(4)**. Studies using this small sample lacked meaningful information on the effects of lengthy bulk holding conditions on actual commercial batches, which are as large as **(b)(4)**.

The **(b)(4)** process is a critical step in the manufacture of **(b)(4)** solid dosage forms. Long hold periods can increase moisture levels, cause aggregation of particles, lead to inconsistent flow characteristics, and promote segregation during **(b)(4)** or **(b)(4)**.

Your firm's response acknowledged that studies should have been conducted using quantities that are representative of the commercial batch operation. However, your response was inadequate because you failed to perform a retrospective assessment of the effect of your excessive hold times on the **(b)(4)** and stability of your drug products. Furthermore, you did not include enhanced controls or interim commitments to ensure that the quality attributes of your products are not affected while you perform studies to support appropriate maximum holding times.

In response to this letter:

- Perform a retrospective review of all batches shipped to the U.S. Place batches with **(b)(4)** held more than **(b)(4)** on the stability program. Provide initial test results (dissolution, content uniformity, and assay) on each such batch within 45 days of receipt of this letter.
- For each batch with an OOS result (whether or not it was later invalidated) since 2014, provide the associated holding times for each significant manufacturing step.
- For each product, perform representative and robust studies to establish appropriate time limits for all significant manufacturing steps.
- Create improved production procedures that prevent future occurrences of unnecessarily long hold times.
- Provide interim procedures that establish in-process hold time restrictions.

Lupin Indore

1. Your firm failed to establish appropriate time limits for the completion of each phase of production to assure the quality of the drug product (21 CFR 211.111).

The studies intended to support **(b)(4)** hold times were inadequate because the holding conditions were not representative of actual operations. Your SOP HT2/004-00, *Hold Time Study Protocol for Compressed or* **(b)(4)** *Tablets as Finished Product,* indicates that a sampling quantity of **(b)(4)** to **(b)(4)** should be collected during your studies, regardless of batch size and drug product. Studies using this small sample lacked meaningful information on the effects of lengthy bulk holding conditions on actual commercial batches, which ranged from approximately **(b)(4)** to **(b)(4)** in size.

In your response, you committed to full-scale hold time studies for products with **(b)(4)** stages that you consider "high risk."

However, your response was inadequate because you failed to perform a retrospective assessment of the effects of long hold times on the **(b)(4)** and stability of all your drug products. Furthermore, you did not include any interim measures or commitments to ensure that the quality attributes of your products are not affected while you create more appropriate hold times.

In response to this letter:

- Perform a retrospective review of all batches shipped to the U.S. Place batches with **(b)(4)** held more than **(b)(4)** on the stability program. Provide initial test results (dissolution, content uniformity, assay) on each such batch within 45 days of receipt of this letter.
- For each batch with an OOS result (whether or not it was later invalidated) since 2014, provide the holding times for each significant manufacturing step.
- For each product, perform representative and robust studies to establish appropriate time limits for all significant manufacturing steps.
- Create improved production procedures that prevent unnecessarily long hold times in the future.
- Provide interim procedures that establish in-process hold time restrictions.

2. 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 or not the batch has already been distributed (21 CFR 211.192).

Your firm invalidated initial OOS laboratory results without adequate investigations. From January 1, 2015, to December 31, 2016, you invalidated nearly all (134 out of 139) initial OOS results and attributed them to laboratory error. Although some investigations failed to clearly establish that laboratory error occurred, you did not conduct a full-scale investigation to thoroughly review potential manufacturing causes and assess commercial history to identify similar instances of high variation or OOS results.

For example, you opened laboratory investigation OOS/C/16/IN2/FP/011 after obtaining an OOS finished product assay result of **(b)(4)**% (release testing specification: **(b)(4)**–**(b)(4)**%) for **(b)(4)** tablets USP **(b)(4)** mg, batch **(b)(4)**. You discarded the original vial that yielded the OOS result, which violates your OOS procedure. Testing of stock solutions, including **(b)(4)** and re-dilution, yielded slightly higher passing results (**(b)(4)**%, **(b)(4)**%, **(b)(4)**%). Based on a triplicate retest, you invalidated the initial failing result without investigating the potential manufacturing root causes.

You had also obtained a low assay result for batch **(b)(4)**, and again reported passing retest results without an investigation of potential manufacturing causes of the OOS assay result.

Your CAPA have often been limited to retraining your analysts. Improvements in analytical methods and equipment were not generally implemented to enhance robustness and prevent errors.

In your response, you committed to track and trend OOS results to identify specific tests and analysts who may be sources of the root cause. Additionally, you stated that your process for invalidating an OOS result and accepting retest results will be more rigorous.

We acknowledge your improvements in human error risk mitigation and tracking OOS trends to identify more sustainable solutions. We also note that you are endeavoring to improve your OOS procedures. However, your response was inadequate because your investigation procedure did not appear to be sufficiently remediated. You also did not perform a retrospective assessment to identify all OOS results which were invalidated without strong scientific justification and clear evidence. Furthermore, your response did not review production to determine whether OOS results were due to potential problems in manufacturing (e.g., in-process hold times), rather than an assumed laboratory cause.

In response to this letter, provide an independent assessment of Lupin Indore, including:

- All invalidated OOS (in-process and finished testing) results obtained for products on the U.S. market. Assess whether the scientific justification and evidence was conclusive. For investigations that conclusively established laboratory root cause, determine adequacy of the CAPA, and ensure the other laboratory methods that are vulnerable to the same root cause have been identified for remediation. For any OOS that had an inconclusive or no root cause identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of manufacturing steps, process capability, deviation history, batch failure history). Provide a CAPA plan that identifies the potential manufacturing root causes for each such investigation, and includes process improvements where appropriate.
- Historical performance of all laboratory methods. Assess adequacy of instructions for each method, suitability of laboratory equipment, and competency of analysts. Determine errors that have occurred on multiple occasions over the history of the method, and identify further CAPA measures needed to enhance robustness.
- Your overall system for investigating OOS results. Provide a CAPA to improve quality of OOS investigations in all Lupin facilities. Elements of your CAPA should include, but not be limited to, enhanced quality assurance participation in individual laboratory investigations and in identifying adverse laboratory control trends.

Also provide your updated laboratory investigation procedure. Describe how your revised procedure ensures that all OOS investigations extend to a full review of potential manufacturing root causes whenever a cause is not conclusively found in the laboratory.

For more information about handling failing, OOS, out-of-trend, or other unexpected results, and documenting investigations, see FDA's guidance document, *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*, at **https://www.fda.gov/downloads/drugs/guidances/ucm070287.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm070287.pdf)**.

CGMP Consultant Recommended
Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements. In particular, the consultant should comprehensively assess your manufacturing processes and laboratory systems, and retrospectively review all OOS investigations. Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

Repeat Observations at Multiple Sites
FDA cited similar CGMP observations at these facilities in your company's network.

- On March 11, 2016, Lupin Limited Goa, FEI 3004819820, was cited for, among other items, invalidating OOS results without thorough investigations.
- On January 23, 2015, Lupin Limited Indore, FEI 3007549629, was cited for, among other items, invalidating OOS results without thorough investigations.

These repeated failures at multiple sites demonstrate that your company's oversight and control over the manufacture of drugs is inadequate. You should immediately and comprehensively assess your company's global manufacturing operations to ensure that systems and processes, and ultimately, the products manufactured, conform to FDA requirements at all your sites.

Conclusion
Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations in all your facilities.

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) 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 applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations may also result in FDA refusing admission of articles manufactured at Lupin Limited at 15-B, Phase 1A, Verna Industrial Area, Verna, Salcette, Goa, and Lupin Limited at Unit 2–Plot No. 2, SEZ Phase-II, Misc., Apparel Park, District Dhar, Pithampur, Indore, Madhya Pradesh, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles 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 inspections 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:

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