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 ORAPHARMInternational483responses@fda.hhs.gov	09/06/2021-09/18/2021
	FEI NUMBER 3004819820

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Srinivas Rao Kalakuntla, Vice President & Site Head - Manufacturing

FIRM NAME	STREET ADDRESS
Lupin Limited	B-15, Phase 1A, Verna Industrial Area
CITY, STATE, ZIP CODE, COUNTRY Verna, Salcette, Goa – 403722, India	TYPE ESTABLISHMENT INSPECTED Drug Product 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

Investigations of an unexplained discrepancy did not extend to other drug products that may have been associated with the specific failure or discrepancy.

Specifically,

a. An OOT/GA/20-054-CS was initiated on 8/12/2020 to probe the border line assay results recorded for (b) (4) Tablets (b) (4) mg, (b) (4) Tablets (b) (4) mg, and (b) (4) Tablets (b) (4) mg under the stability (**Table 1**). You invalidated the initial results (**Table 1**, Initial Assay data, OOT) through re-testing and reported the average results of replicate retests (**Table 1**, Retest Assay data).

Table 1. Assay test data for (b) (4) Tablets

Entry	Batch No.	Strength	Stage	Assay data		
				Initial*	Retest**	Δ
(b) (4)						

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(b) (4)

*OOT assay test data from (b) (4) brand (b) (4) ; **Retest data from (b) (4) brand (b) (4) Δ Difference between the Retest and Initial % assay.

Through the hypothesis, you confirmed that the (b) (4) brand (b) (4) used in the initial assay was the root cause for lower assay data. On average, (b) (4) brand (b) (4) gave a (b) (4) % lower value for the assay test. The investigation report suggested laboratory error as the root cause and stated that "The OOS results are due to usages of (b) (4) make during analysis which might have affected the extraction of product". However, this conclusion was not verified/supported by any scientific rationale.

On 9/10/2021, your Senior General Manager, Head Investigations (Corporate Quality) shared Certificate of Analysis for (b) (4) brand (b) (4) and stated that a quality difference in the two brands of HPLC grade (b) (4) was the reason for observed assay test results. Your Senior General Manager, Quality Assurance shared a report "OOT-GA-20-054-CS file Note, Dated 9/9/2021" that further stated that the %transmission (at (b) (4) nm) for (b) (4) brand (b) (4) is (b) (4) % whereas for the (b) (4) the %transmission is (b) (4) %. This document states that "Difference in transmittance at wavelength (b) (4) nm could be a probable cause for the lower results in assay test in OOT no. OOT/GA/20-054-CS". We noted that the Assay test (STP No. STP-1213-05, Effective date 11/26/2019) is carried out at (b) (4) nm.

According to a report, "Purchase order of (b) (4) ' submitted by your Senior General Manager, Quality Assurance, you purchased (b) (4) f HPLC grade (b) (4) brand (b) (4) on (b) (4) On 4/17/2020, this (b) (4) was issued to the quality control department. You have no electronic records to trace the (b) (4) brand (b) (4) hat was used in your firm (Lupin Goa site) for the testing of drug products and/or drug substances. You manufactured and shipped at least (b) (4)

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drug products to the US market and (b) (4) is used in the analytical test methods for at least (b) (4) drug products made for the US market. Your investigation did not extend to review the test data for the drug products that are manufactured at the firm including at least (b) (4) drug products for the US market whose analytical testing required HPLC grade (b) (4).

b. An OOS-C-19-GA-FP-027 was initiated on May 13th, 2019 to probe an OOS results for content uniformity for (b) (4) Tables USP (b) (4) mg Batch No. (b) (4) or the US market (**Table 2**). This batch was used in the manufacturing of (b) (4) TAB USP (b) (4) MG-(b) (4) (US) Batch No. (b) (4) Manufacturing date (b) (4) Expiry date (b) (4). On (b) (4) you shipped (b) (4) units (b) (4) tablets) to US.

Table 2. Content Uniformity data for OOS Batch

Batch No. (b) (4)	Average	Minimum	Maximum	Acceptance Value
Specification	Acceptance Value NMT (b) (4)			

According to your investigation, the laboratory error was the root cause whereby during the final preparation of the "sample for analysis" contributed to the OOS. More specifically, the error probably happened during (b) (4) during the preparation of HPLC analysis sample.

According to the investigation, the analyst prepared the test samples by following the test procedure, STP-0123-10 that included (b) (4) The samples were then analyzed on HPLC (b) (4) batches in that order. It was the second/middle batch, (b) (4) that recorded an OOS results for content uniformity.

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Your investigation reads, "***the analyst suspects that she inadvertently did not (b) (4) (b) (4) This means, out of (b) (4) remaining batches, sample solution of (b) (4) batch would not have been (b) (4) properly. Thereby resulting in OOS for Batch No. (b) (4) ***".

There is no scientific rationale that (b) (4) when the analyst followed the STP-0123-10 that involved (b) (4) There is no evidence that the drug product can come out of the (b) (4) Even though, initially the laboratory investigation was not conclusive, you did not investigate the manufacturing process as per Section 5.1.15 of your procedure, SOP_MUM_CQA_019647(2.0) Handling of OOS Test Results.

OBSERVATION 2

In process materials are not tested for strength and approved or rejected by the quality control unit during the production process.

Specifically, you didn't conduct in-process testing for (b) (4) . Your firm changed the batch size for (b) (4) for (b) (4) (b) (4) mg, (b) (4) mg, and (b) (4) mg from (b) (4) You co idation for (b) (4) batch size. As per your Process Validation Protocol (VP/111-08 effective date 3/9/2009) and Process Validation Report (VP/11-08, effective date 4/18/2009) you did conduct the (b) (4) for the three validation batches but you do not conduct the same for the manufacturing batches. Your In-process control for (b) (4) batch no. (b) (4) only includes testing for (b) (4) You recorded (b) (4) % for the (b) (4) for (b) (4) (b) (4) mg, (b) (4) mg, and (b) (4) mg from (b) (4)

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OBSERVATION 3

Your examination and testing of samples did not assure that the drug product and in-process material conformed to specification.

Specifically, during walkthrough of your tablet manufacturing Room No. (b) (4) (in Unit (b) (4)), we observed 99 tablets in a bowl on the balance PR-BAL-207. We also saw about 80 tablets discarded in a bin next to the balance. In addition, (b) (4) g of the tablets were discarded from the initial setup of the machine.

In Room No. (b) (4) (Unit (b) (4) you were manufacturing (b) (4) tablets (b) (4) mg, Batch No. (b) (4) on tablet press machine, PR-TCM-002 for US market. According to the equipment status board, you recorded the group weight for (b) (4) tables at 11.04.23 am on 9/14/2021 and then next group weight was due in (b) (4) On questioning the reason to have 99 tables in a bowl on the balance, PR-BAL-207, your production supervisor stated that he conducted two additional group weights with (b) (4) tablets each. The production supervisor also said that the machine operator also took an additional group weight. The machine operator stated that he took one group weight for the tablets. However, the production supervisor and machine operators were unable to produce a document and/or record for these additional group weights data. The production supervisor was unable to account for all the 99 tables that was stored in the bowl on the balance, PR-BAL-207 in Room No. (b) (4) (Unit (b) (4).

Your VP, Manufacturing stated that the operator followed the procedure SOP_GA_PR_002384 (3.0), Operation of Tablet (b) (4) (MRC-36N) (PR-TCM-002), when he made additional tests and did not record it. The Section 5.4.46 of the procedure had provision for additional tests outside of the In-process test. However, your VP, Manufacturing did not provide any evidence/document that suggested the machine needed any fine adjustment.

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OBSERVATION 4

Establishment of the reliability of component supplier's report of analysis is deficient in that the test results are not appropriately validated at appropriate intervals.

Specifically, we observed the tests not being completed but results reported from the manufacturer Certificate of Analysis (COA) without your firm validating the test results at an appropriate interval.

Your firm has approximately (b) (4) active and (b) (4) inactive pharmaceutical ingredients for commercial manufacturing for the US market. The validation of test results has not been conducted for approximately (b) (4) active and (b) (4) for inactive ingredients. Test results that are taken from the manufacturer COA for active and inactive ingredients may include but are not limited to: (b) (4) (b) (4) X-ray diffraction, limit/content of (b) (4)

For example, between January 2018 to 17th September 2021, your firm has received (b) (4) lots of (b) (4) USP active pharmaceutical ingredient and uses the results from the manufacturers COA but has no record of the validation of the test results from the manufacturer. Below are additional examples of active and inactive drug components for the same timeframe for which the validation of the test results has not been conducted.

- Approximately (b) (4) lots (b) (4) USP received and released based on the manufacturer results for (b) (4) impurities (By (b) (4) (ppm). Between February 2019 and September 2021, your firm has manufactured and shipped to the US approximately (b) (4) lots of drug product that contain (b) (4)
- Approximately (b) (4) lots of (b) (4) USP received and released based on the manufacturer results for limit of (b) (4) particle size, and bulk density. Between February 2019 and September 2021, your firm has manufactured and shipped to the US approximately (b) (4) lots of drug product that contain (b) (4)
- Approximately (b) (4) lots of (b) (4) USP were received and released based on the manufacturer results for limit of (b) (4) Records show that (b) (4) USP batch (b) (4) was

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used in the manufacture of approximatelv (b) (4) finished drug products which may include, (b) (4) capsules (b) (4) mg and (b) (4) tablets USP (b) (4) mg.

- Approximately (b) (4) ots for (b) (4) (Material Code: (b) (4) and (b) (4) lots for (b) (4) Material Code: (b) (4) received and released based on the manufacturer (b) (4) respectively. Records show that (b) (4) batch (b) (4) were used in the manufacture of approx (b) (4)

Your firm's reduced testing program (SOP_MUM_CQA_008553 (2.0) and SOP_GA_QC_005434 (3.0)) requires (b) (4) The full testing does not include performing all tests. As per some of your testing procedures, the manufacturer's results are reported as part of the (b) (4) When the (b) (4) is conducted if the equipment necessary to conduct testing is not available, the qualit raw material procedure (SOP_GA_QC_005434 (3.0)) allows for the result to be taken from the manufacturer COA.

Your vendor qualification does not have a requirement for appropriate validation of the supplier's test results at appropriate intervals. There is no quality procedure detailing the requirement to validate the supplier test results at an appropriate interval.

OBSERVATION 5

The procedures for annual quality standards record evaluation are deficient in that they do not address a review of returned drug product records for each drug product.

Specifically, none of your annual product review for the US market include products returned. Between February 2019 and September 2021, there have been approximately 1,475,525 returned bottles/box. The drug products returned include but are not limited to; (b) (4) Tablets (b) (4) mg lot (b) (4) (b) (4) Tablets USP (b) (4) mg Lot (b) (4) (b) (4) Suspension USP (b) (4) mg (b) (4) mL.

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The quality agreement with the company responsible for distribution does not include a requirement for the documentation of returns or the process by which the returns are communicated. Your quality unit fails to have adequate procedures to assure the returns are captured in the annual product review. There has been no assessment into any potential quality related issues for the returns.

OBSERVATION 6

The written stability program is not followed.

Specifically, we observed one fully sealed and two partially sealed bottles for protocol NRP/21/84-00 and the stability protocol is for (b) (4) The protocol (NRP/21/84-00) is a monitoring study of the effect of open seals and partially open seals for (b) (4) Suspension USP (Pack size (b) (4) mL) Batch No. (b) (4) on (b) (4) and microbial limit test (MLT). This study was being conducted as part of a corrective action for partially open seals found in retain samples.

OBSERVATION 7

Access to the storage area for labels and labeling materials is not limited to authorized personnel.

Specifically, during the walkthrough of the Unit (b) (4) nd Unit (b) (4) warehouse area, we observed labels and labeling materials were stored on the shelfs. These labeling materials were easily accessible to anyone in the warehouse. The labels were not stored under a lock and key and the section of the warehouse where labels were stored was not equipped with access control equipment and the area was freely accessible to anyone in the warehouse.