DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
ORA OPQO HQ, Room #2032 12420 Parklawn Drive, Rockville, MD 20857 ORAPHARMInternational483responses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	01/28/2019-02/08/2019
	FEI NUMBER 3004819820

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Srinivas Rao Kalakuntla, Senior General Manager & 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

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,

1. The firm's procedure CQA-004-17 "Handling of out of Specification test results" Section 5.1.12 (a) states – 'Retesting shall be done by (b) (4) analysis following the approved laboratory procedure preferably by original analyst from the portion of sample available in the laboratory'. The procedure lacks statistical justification to release the batch based on (b) (4) retest data.

   a) OOS/C/18/GA/FP/042 was initiated on April 09, 2018 to probe the failure in assay for (b) (4) in (b) (4) and (b) (4) tablets USP (b) (4) mg / (b) (4) mg, Batch Nos. (b) (4) ((b) (4) %) and (b) (4) ((b) (4) %) against a specification limit of (b) (4) % to (b) (4) %. The initial samples of batch (b) (4) and (b) (4) prepared on April 06, 2018 were then reinjected, re-vialed and injected after re-dilution on April 09, 2018 without establishing system precision as part of hypothesis test. Based on passing result obtained from re-dilution, the root cause was identified as dilution error and (b) (4) new sample was prepared on April 13, 2018. The results tabulated below do not substantiate the area response obtained for standard and sample during hypothesis and sample retest. Also, the impact of standard response on the assay result was not evaluated. Approximately +4% bias was observed in the area response between the initial (b) (4) vs fresh (b) (4) standard responses. However, the sample response for initial preparation and (b) (4) confirmatory

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preparation were consistent to the sample weights. The review of OOS by your third-party consultant concluded that the root cause determined was unsatisfactory, however finally concurred with the firm's investigation.

Batch	Initial Assay%	Hypothesis			Fresh preparation
		Reinject	Re-vial	Re-dilute	
(b) (4)	(b) (4)				
Standard weight	(b) (4) mg		(b) (4) mg		(b) (4) mg
Standard response	(b) (4)		(b) (4)		(b) (4) (+4%)
Sample weight Batch (b) (4)	(b) (4) mg		(b) (4) mg		(b) (4) mg
Sample response Batch (b) (4)	(b) (4)				
Sample weight Batch (b) (4)	(b) (4) mg		(b) (4) mg		(b) (4) mg
Sample response Batch (b) (4)	(b) (4)				

These batches (b) (4) and (b) (4) were released to US market based on (b) (4) confirmatory test.

b) OOS/C/17/GA/FP/144 was initiated on December 13, 2017 to probe the failure in unknown impurity ((b) (4) %) at relative retention time (RRT) of (b) (4) for (b) (4) Capsules, (b) (4) mg batch (b) (4) against a specification limit of (b) (4) %. On reinjecting the same initial vial as part of hypothesis study, no peak was observed at RRT (b) (4) however a new peak was observed at RRT (b) (4). Then, a fresh sample preparation was injected and a peak was observed at RRT (b) (4) ((b) (4) %), however it was named as Impurity (b) (4). Per test procedure Impurity (b) (4) elutes at RRT (b) (4). The molecular mass of impurity peak was identified at R&D and based on the molecular mass the

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impurity was assumed to be coming from (b) (4) and on injection of (b) (4) standard, the peak for (b) (4) eluted at RRT (b) (4) The investigation concluded that the OOS for unknown impurity at RRT (b) (4) is due to (b) (4) contamination attributing the failure to Analyst error whereas (b) (4) peak elutes at RRT (b) (4) The batch was released to US market based on new (b) (4) sample preparation made on 5th March 2018 wherein no peak eluted at RRT (b) (4) but a peak at RRT (b) (4) (b) (4) %).

2. The investigation (DEV-GO-276-18-0061) conducted on (b) (4) Tablets USP (b) (4) (b) (4) mg, batch (b) (4) (Expiry July 2020) was found deficient. (b) (4) spots were observed over the finished drug product during the AQL check performed (b) (4) manual inspection. Based on the finding, the batch was manually inspected again, and all together separated 224957 defective tablets out of (b) (4) tablets. The (b) (4) batch yield inclusive of manufacturing loss (b) (4) %) did not meet the batch record specification limit of (b) (4) % to (b) (4) %. Your investigation concluded that the (b) (4) spots were possibly from the (b) (4) due to improper (b) (4) at (b) (4) stage. However, no qualitative test was performed to confirm that the spots were from the (b) (4) to rule out other contaminants. The batch was released to US market.

OBSERVATION 2

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Specifically,

As per the approved batch records, the (b) (4) procedure is required to be continued (b) (4) (b) (4) without a discharge process of the (b) (4) However, during manufacturing, the (b) (4) is discharged into smaller bins (b) (4) procedure. Currently, the discharge process is documented in additional data entry pages which are not part of approved batch records. An evaluation of

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discharge process and the (b) (4) uniformity after discharging into bins has never been studied as part of the process validation. In addition, this procedure is performed without raising a deviation which is required as per SOP # CQA-003-06, entitled as "Handling of Deviations". This deviation from approved batch records were observed for the following products, but not limited to

Product	Number of batches	Shipped to US market since
(b) (4) Tablets USP, (b) (4) mg	(b) (4)	February 2017
(b) (4) Tablets USP, (b) (4) mg		February 2017
(b) (4) Tablets USP, (b) (4) mg		February 2012
Tablets USP, (b) (4) mg		April 2012
(b) (4) Tablets USP, (b) (4) mg		March 2014
Tablets USP, (b) (4) mg		March 2014
Tablets USP, (b) (4) mg		March 2014
(b) (4) Capsules, (b) (4) mg		December 2013

***DATES OF INSPECTION**

1/28/2019(Mon), 1/29/2019(Tue), 1/30/2019(Wed), 1/31/2019(Thu), 2/1/2019(Fri), 2/4/2019(Mon), 2/5/2019(Tue), 2/6/2019(Wed), 2/7/2019 (Thu), 2/8/2019(Fri)

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