DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave,Bldg 51,Rm 4225 Silver Springs, MD 20993 (301) 796-3334 Fax:(301) 847-8738 Industry Information: www.fda.gov/oc/industry	07/09/2015 - 07/17/2015
	FEI NUMBER 3004819820

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Alok Ghosh, President Technical Operations

FIRM NAME	STREET ADDRESS
Lupin Limited	15-B, Phase 1A, Verna Industrial Area
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Verna, Salcette, Goa 403 722, India	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:

LABORATORY CONTROL SYSTEM

OBSERVATION 1

Drug products failing to meet established specifications and quality control criteria are not rejected.

Specifically, the following batches generated OOS results and failed in-process (IP) specifications; however, the finished product batches were released by the quality control unit (QCU) and distributed without invalidating the IP OOS results, as listed below. Finished product batch (b) (4) was not distributed.

Product	IP Batch#	IPC test	Batch Record	Released?	Packaging Batch Record	Released and Distributed?	Date of Release	Batch Size (Tabs)
(b) (4)				Yes	(b) (4)	Yes	(b) (4)	
				Yes		Yes		
				Yes		Yes		
				Yes		Yes / Yes		
				Yes		Yes / Yes		
				Yes		Yes/Yes		
				Yes		Same as above		
				Yes		Yes/No		

Additionally, IP (b) (4) batch (b) (4) failed the average assay value for (b) (4) and (b) (4) (% and (b) (4) %, respectively, filed specification (b) (4) % to (b) (4) %. This batch was (b) (4) to make the finished product batch (b) (4). The QCU rejected batch (b) (4) because it did not meet the finished product specification, FPS-0245-02. There is no mention in the final batch disposition that links the rejection of the final batch due to an IP specification failure.

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Luis A. Dasta, Investigator
Charanjeet Jassal, Investigator

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OBSERVATION 2

Reserve samples from representative sample lots or batches of drug products selected by acceptable statistical procedures are not examined visually at least once a year for evidence of deterioration.

Specifically, the QCU does not conduct visual examination of reserve samples of drug products on an annual basis for evidence of deterioration. SOP SAP-099-01, eff. date of 5 Aug 2013, Annexure V, (b) (4) tablets, states that (b) (4)

QUALITY SYSTEM

OBSERVATION 3

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,

a) Over 40 complaints (e.g. suspension (b) (4) related to different batches the (b) (4) suspension (b) (4) mg (b) (4) mL & (b) (4) mg (b) (4) mL (e.g. batches (b) (4) had been reported and investigated since product launch in (b) (4). However, the investigations were not thorough as they did not include:

1) a thorough multi-attribute assessment of the product and impact on product quality as the product is routinely used by patients (e.g. (b) (4) assay, and dissolution each time that the bottle is open for dosing purposes and a dose is poured out of the bottle for the duration of the treatment, up to (b) (4)

2) a thorough evaluation to determine whether the complaint samples, reportedly received with diluent leaks by the quality control unit, were the result of mishandling of the product during shipping or the result of packaging quality issues;

3) thorough evaluation of the firm's identified most probable root cause (i.e., patients did not follow instructions of (b) (4)). No investigational testing (e.g. assay from the top and bottom of the suspension, deliverable volume, dissolution) of each dose over a period equivalent to the duration of treatment was conducted in order to demonstrate that the hypothesis has merit. In addition, the investigation did not evaluate (e.g. (b) (4) (b) (4) to replicate and evaluate the firm's identified most probable cause;

4) an evaluation of an unexplained discrepancy (i.e., the relatively (b) (4) (b) (4) thus indicating a suitable suspension, vs. the observed phenomenon of samples of the complaint product (b) (4) int (b) (4) and diluent within (b) (4); and

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Luis A. Dasta, Investigator LAD Charanjeet Jassal, Investigator CJ	DATE ISSUED 07/17/2015

5) evaluation of the specifications to determine whether new specifications need to be established or the current specifications such as (b) (4) need to be revised as it was evident by the number and nature of complaints that the current specifications did not provide meaningful information/data about a product that was (b) (4) upon patient use.

A number of (b) (4) batches were manufactured and released since (b) (4) In Sep 2014, (b) (4); after launching the product, the firm stopped manufacturing the product but did not conduct an evaluation to assess the need for a market action decision even though the firm (b) (4) (b) (4)

b) Investigation OOS/C14/GA/FP/192 was initiated on 11 Nov 2014. As per your SOP on handling OOS investigations, on 12/22/14 (within (b) (4) you initiated a blanket extension for the noted investigation to 28 Feb 2015. The investigation was not completed by 28 Feb, and no further extension was made on or before that specified date. On 7 Mar 2015, the QCU initiated another extension for the same investigation to 15 Apr 2015. The gap/oversight between the completion of the first extension and the initiation of the second extension could not be explained by the QCU. Additionally, your SOP CQA-004-08, eff. date 24 Nov 2014, section 5.9.3, states that an OOS may be given up to (b) (4) extensions prior to completion; however, there is no maximum timeframe specified in the SOP for the extensions so that investigations can be closed in a timely manner. The following OOS investigations were noted as having a closure date of approximately 6 months or greater:

OOS Investigation No.	Date of Occurrence	Date of Closure
OOS/C/15/GA/RM/002	Jan. 3rd 2015	Still Open
OOS/C/15/GA/RM/034	Jan. 31st 2015	Still Open
OOS/C/14/GA/IP/017	Feb. 6th 2014	Nov. 29th 2014
OOS/C/14/GA/FP/032	March 6th 2014	Nov. 14th 2014

FACILITIES AND EQUIPMENT SYSTEM

OBSERVATION 4

Input to and output from the computer, related systems of formulas, and records or data are not checked for accuracy.

Specifically, the SCADA software/hardware electronic system used to enter in-process checks (e.g. (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) in addition to other functions, is not checked at a suitable frequency for accuracy to ensure outputs are accurate and unaffected.

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OBSERVATION 5

The separate or defined areas and control systems necessary to prevent contamination or mix-ups are deficient.

Specifically, defined processing areas (e.g.(b) (4) compression, and capsule filling) and control systems (i.e., cleaning of the defined areas with(b) (4) and non-dedicated mops; mops are not replaced at suitable intervals; and cleaning frequency of defined processing areas and main floor corridors(b) (4)) are deficient. The firm's staff manufactures drug products or(b) (4) yet the cleaning schedule of the processing areas and corridors (b) (4). There was no data/information to justify this type of cleaning frequency. In addition, there was no data/information to justify the use of non-dedicated mops, the frequency of mops replacement (e.g. (b) (4) and the use of(b) (4) to clean the aforementioned defined areas. In light of the noted deficiencies, the flow of materials and personnel through the building is not designed to prevent contamination as materials and personnel can enter/exit non-dedicated processing areas onto the non-dedicated corridors at all times without gowning changes or other control system to minimize cross-contamination.

OBSERVATION 6

Written procedures are not followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

Specifically, SOP SAP-064-08, eff. date 3 Mar 2015, Cleaning Validation and Verification of Equipment, states that manufacturing equipment shall be cleaning-verified(b) (4) However, your records for tablet compression equipment PR-TCM-011 indicate that this equipment was cleaning-verified on January 2014, December 2014 and April 2015.

OBSERVATION 7

Records are not kept for the cleaning and sanitizing of equipment.

Specifically, records are not kept for the cleaning of non-dedicated(b) (4) used in(b) (4) quipment for the manufacture of different products (e.g.(b) (4) Capsules,(b) (4) Suspension(b) (4) Tablets,(b) (4) Capsules,(b) (4) Tablets, and(b) (4) Tablets).

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PRODUCTION SYSTEM

OBSERVATION 8

Control procedures are not established which monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

Specifically, no content uniformity is conducted to monitor the output and validate the performance of the compresion of tablets or filling of capsules manufacturing processes of drug products for which the (b) (4) as follows:

Product	Strength (mg)	Net weight of dosage form (mg)	(b) (4)
(b) (4) Capsules	(b) (4)	(b) (4)	(b) (4)
Capsules			
Capsules			
(b) (4) ablets			
Tablets			

In addition, the quality control unit conducts finished product content uniformity testing on (b) (4) dosage units regardless of the batch size.

MATERIALS SYSTEM

OBSERVATION 9

Written procedures are not followed for the storage and handling of components.

Specifically, (b) (4) USP, batch (b) (4) total of (b) (4) containers, was to be stored in (b) (4) locations in the warehouse for raw materials as per SAP entries made by the warehouse staff. Location (b) (4) was scanned, and (b) (4) containers of this raw material were confirmed on a pallet. Location (b) (4) was supposed to have (b) (4) containers of this raw material, but instead, it had (b) (4) containers of (b) (4) USP, batch (b) (4) Location (b) (4) was supposed to have the remaining (b) (4) containers of (b) (4) but instead, it had the (b) (4) conatiners of (b) (4) that were supposed to be in location (b) (4). The warehouse staff failed to store the containers as per the firm's procedures. There is no assurance that raw materials stored in the raw materials warehouse are stored in their assigned locations to prevent mixups.

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