

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 10903 New Hampshire Ave, Bldg 51, Rm 4225 Silver Springs, MD 20993 (301) 796-3334 Fax: (301) 847-8738	DATE(S) OF INSPECTION 6/12/2017-6/16/2017
	FEI NUMBER 3009107538

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Amit Sareen , Site Head and VP of Manufacturing

FIRM NAME Lupin Limited	STREET ADDRESS Unit 3, Plot No. M-1, SEZ, Phase II,, Misc Zone, Apperal Park, Dist Dhar,
----------------------------	--

CITY, STATE, ZIP CODE, COUNTRY Pithampur, Madhya Pradesh, 454 775 India	TYPE ESTABLISHMENT INSPECTED Manufacturing
--	---

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 whether or not the batch has been already distributed.

Specifically,

Your firm has invalidated 87% of the OOS for (b) (4) used in (b) (4) from 2015 to 2017. For example:

(A) OOS Investigation OOS/E/16/IN3/SS/002 was initiated on Jan 8, 2016 to find the 3 months accelerated stability (b) (4) content uniformity (b) (4) (inter- (b) (4) content uniformity) and (b) (4) content uniformity (b) (4) failure for (b) (4) (b) (4) mcg (equivalent to (b) (4) mcg (b) (4) Base) per (b) (4), Batch (b) (4). Failing (b) (4) result of (b) (4) % and (b) (4) result of (b) (4) % for (b) (4) (b) (4) orientation) was obtained against the specification limit for (b) (4) and (b) (4) testing. Your conclusion was assumed and not made on the basis of scientific evaluation. Your invalidated the initial results through retesting next subsequent (b) (4) and reported the (b) (4) results of these (b) (4). The investigation did not extend to review of the manufacturing process to ascertain if the (b) (4) issues were attributed by the manufacturing process. Batch (b) (4) is an exhibit batch filed in support of (b) (4) (b) (4)

(B) OOS Investigation OOS/E/16/IN3/SS/018 was initiated on June 28, 2016 to find the 9 months long term stability (b) (4) content uniformity (b) (4) (inter (b) (4) content uniformity) failure for (b) (4) (b) (4) mcg (equivalent to (b) (4) mcg (b) (4) Base) per (b) (4), Batch (b) (4). A failing (b) (4) result of (b) (4) % for 1st (b) (4) of (b) (4) (b) (4) orientation) was obtained

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Doan T Nguyen, Investigator Zhigang Sun, FDA Center Employee or Employee of Other Federal Agencies	<input checked="" type="checkbox"/> Doan T Nguyen <small>Doan T Nguyen Investigator Signed by: Doan T. Nguyen -S</small>	DATE ISSUED 6/16/2017 6/16/2017
---------------------------------	---	---	---------------------------------------

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 10903 New Hampshire Ave, Bldg 51, Rm 4225 Silver Springs, MD 20993 (301) 796-3334 Fax: (301) 847-8738	DATE(S) OF INSPECTION 6/12/2017-6/16/2017
	FEI NUMBER 3009107538

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Amit Sareen , Site Head and VP of Manufacturing

FIRM NAME Lupin Limited	STREET ADDRESS Unit 3, Plot No. M-1, SEZ, Phase II,, Misc Zone, Apperal Park, Dist Dhar,
----------------------------	--

CITY, STATE, ZIP CODE, COUNTRY Pithampur, Madhya Pradesh, 454 775 India	TYPE ESTABLISHMENT INSPECTED Manufacturing
--	---

against the specification limit for (b) (4) testing. Your conclusion was assumed and not made on the basis of scientific evaluation. Your invalidated the initial results through retesting next subsequent (b) (4) and reported the (b) (4) results of these (b) (4). The investigation did not extend to review of the manufacturing process to ascertain if the (b) (4) issues were attributed by the manufacturing process. Batch (b) (4) is an exhibit batch filed in support of (b) (4).

(C) Similar issues are also observed in the following OOS Investigation reports: OOS/E/16/IN3/SS/013 and OOS/E/16/IN3/SS/019 for Batch (b) (4); OOS/E/16/IN3/SS/014 and OOS/E/16/IN3/SS/021 for Batch (b) (4). Both exhibit batches are filed in support of (b) (4).

OBSERVATION 2

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

Specifically,

The in-process tests of (b) (4) during the (b) (4) process are not included into the in-process control specifications as well as the batch records. (b) (4) and (b) (4) are critical quality attributes (CQAs) for this low dose, (b) (4).

OBSERVATION 3

Samples taken of in-process materials for determination of conformance to specifications are not representative.

Specifically,

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Doan T Nguyen, Investigator Zhigang Sun, FDA Center Employee or Employee of Other Federal Agencies	DATE ISSUED 6/16/2017
	<input checked="" type="checkbox"/> Doan T Nguyen Doan T Nguyen Investigator Signed by: Doan T. Nguyen -S	

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 10903 New Hampshire Ave, Bldg 51, Rm 4225 Silver Springs, MD 20993 (301) 796-3334 Fax: (301) 847-8738	DATE(S) OF INSPECTION 6/12/2017-6/16/2017
	FEI NUMBER 3009107538

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Amit Sareen , Site Head and VP of Manufacturing

FIRM NAME Lupin Limited	STREET ADDRESS Unit 3, Plot No. M-1, SEZ, Phase II,, Misc Zone, Apperal Park, Dist Dhar,
----------------------------	--

CITY, STATE, ZIP CODE, COUNTRY Pithampur, Madhya Pradesh, 454 775 India	TYPE ESTABLISHMENT INSPECTED Manufacturing
--	---

Your firm has no documentation to show that the sampling plan listed in Annexure-I (b) (4) Sampling Procedure During (b) (4) Stage) of POP/P3/034-01 Process Performance Qualification Protocol for in-process testing of (b) (4) during (b) (4) process is scientifically justified to be representative of the whole (b) (4) process. The (b) (4) process includes multiple significant events such as (b) (4) of (b) (4) till the (b) (4) as well as (b) (4) of bulk suspension.

OBSERVATION 4

Acceptance criteria for the sampling and testing conducted by the quality control unit is not adequate to assure that batches of drug products meet each appropriate specification as a condition for their approval and release.

Specifically,

Your firm did not establish scientific justification of weight limits standards used in your online Check Weigher (CW-502) equipment used for rejecting (b) (4) lying outside the predefine range of acceptable weight limits. On 12 Jun 2017, I observed (b) (4) standards used to verify the sensitivity of rejecting finished product the online Check Weigher (CW-502) identified in (b) (4) bags as (b) (4) weight”.

OBSERVATION 5

Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

Specifically,

There are no controls to access your firm network shared files where Quality unit information is stored for Unit 3, such as stability information for (b) (4) used in (b) (4). I observed on 12 Jun 2017 the ability by the analysis to access Unit 1 and Unit 2 files from Unit 3 computer. Additionally, the employees from Unit 1 and Unit 2 can access Unit 3 computer files.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Doan T Nguyen, Investigator Zhigang Sun, FDA Center Employee or Employee of Other Federal Agencies	<input checked="" type="checkbox"/> Doan T Nguyen <small>Doan T Nguyen Investigator Signed by: Doan T. Nguyen -S</small>	DATE ISSUED 6/16/2017
	6/16/2017		

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 10903 New Hampshire Ave, Bldg 51, Rm 4225 Silver Springs, MD 20993 (301)796-3334 Fax: (301)847-8738	DATE(S) OF INSPECTION 6/12/2017-6/16/2017
	FEI NUMBER 3009107538

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Amit Sareen , Site Head and VP of Manufacturing

FIRM NAME Lupin Limited	STREET ADDRESS Unit 3, Plot No. M-1, SEZ, Phase II,, Misc Zone, Apperal Park, Dist Dhar,
----------------------------	--

CITY, STATE, ZIP CODE, COUNTRY Pithampur, Madhya Pradesh, 454 775India	TYPE ESTABLISHMENT INSPECTED Manufacturing
---	---

6/16/2017

X Zhigang Sun
 Zhigang Sun
 FDA Center Employee or Employee of Other F...
 Signed by: Zhigang Sun -5

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Doan T Nguyen, Investigator Zhigang Sun, FDA Center Employee or Employee of Other Federal Agencies	DATE ISSUED 6/16/2017
		X <u>Doan T Nguyen</u> Doan T Nguyen Investigator Signed by: Doan T. Nguyen -5