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	5/8/2017-5/19/2017*
	FEI NUMBER 3007549629

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
TO: Amit Sareen , Site Head and Vice President - Manufacturing	
FIRM NAME Lupin Limited	STREET ADDRESS Unit 2 - Plot No. 2, SEZ Phase II, Misc., Apparel Park, District Dhar, Pithampur
CITY, STATE, ZIP CODE, COUNTRY Indore, Madhya Pradesh, 454775 India	TYPE ESTABLISHMENT INSPECTED Drug 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 whether or not the batch has been already distributed.

Specifically, your firm has invalidated approximately 96% of all the Out-of-Specification (OOS) results obtained during the testing of commercial drug products during the last two years as summarized below:

Type of Sample	Total # of OOS Obtained in 2015 & 2016	# of invalidated OOS in 2015 & 2016	% invalidated OOS in 2015 & 2016
Commercial stability Samples	33	32	97
In-process Samples	43	40	93
Finished product Samples	62	61	98

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Tamil Arasu, Investigator Darren S. Brown, Investigator	5/19/2017

Hold-Time Sample	1	1	100
Total	**139**	**134**	**96**

Among the invalidated OOS results more than 75% of them were attributed to human error which raises concerns about the ability of your laboratory personnel to properly conduct the required analytical testing. For example,

a) OOS investigation, OOS/C/16/IN2/SS/005 was initiated on 11-May-2016 to find the 18-month long-term stability assay failure for (b) (4) Tablets, USP (b) (4) mg. A failing assay result of (b) (4) % was obtained against a specification limit of (b) (4) % to (b) (4) % of label claim. Your firm invalidated the failing result through re-testing and attributing the failed result to solution preparation error. Your firm has attributed similar solution preparation errors to OOS results 26 times during the last two years and OOS results were invalidated.

b) OOS investigation, OOS/C/16/IN2/FP/011 was initiated on 22-April-2016 to find the assay failure for the finished product (b) (4) Tablets, USP (b) (4) mg (Batch# (b) (4) & (b) (4) . Failing assay results of (b) (4) % and (b) (4) % respectively were obtained against a specification limit of (b) (4) % to (b) (4) % of label claim. Your firm invalidated the failing result through re-testing and attributed it to dilution error during sample preparation. Your firm has attributed similar dilution error to OOS results 19 times during the last two years and OOS results were invalidated.

c) OOS investigation, OOS/C/15/IN2/SS/007 was initiated on 08-April-2015 to find the 30-month stability assay failure for (b) (4) and (b) (4) Tablets, USP (b) (4) (b) (4) mg. A failing assay result of (b) (4) % was obtained against a specification limit of (b) (4) % to (b) (4) % of label claim for (b) (4) Your firm invalidated the failing result through re-testing and attributed it to

(b) (4) error during sample preparation. Your firm has attributed similar (b) (4) error to OOS results 9 times during the last two years and OOS results were invalidated.

d) OOS investigation, OOS/C/15/IN2/SS/002 was initiated on 21-February-2015 to find the 18-month stability dissolution failure for (b) (4) Tablets, USP (b) (4) mg. A failing dissolution result of 5% was obtained in 15 minutes against a specification limit of NLT (b) (4) %. Your firm invalidated the failing result through re-testing and attributed to vial filling error during sample preparation. Your firm has attributed sample preparation error to OOS results 8 times during the last two years and OOS results invalidated.

e) OOS investigation, OOS/C/15/IN2/FP/019 was initiated on 19-June-2015 to find the finished product assay failure for (b) (4) Tablets, USP (b) (4) mg. A failing assay result of (b) (4) % was obtained against a specification limit of (b) (4) % to (b) (4) % of label claim. Your firm invalidated the failing result through HPLC peak re-integration and attributed to contamination error. Your firm has attributed similar contamination error to OOS results 9 times during the last two years and OOS results were invalidated.

You have failed to take timely corrective actions to prevent repeated human errors and attributed these errors to invalidate out of specification results.

OBSERVATION 2

Written records of investigations into unexplained discrepancies do not include the conclusions and follow-up.

Specifically, your firm conducted an investigation into why the (b) (4) materials going through the manufacturing process of (b) (4) and (b) (4) Tablets USP (Batch# (b) (4) and (b) (4)) were kept in quarantine area for more than (b) (4) The root cause in the delay in performing the re-

maining steps of the manufacturing processes was attributed to human error in failing to track the subsequent process steps such as (b) (4) activity. However, during the interview, your firm's Site Head stated that if there are not sufficient orders or demands for a specific product are low, it may take a longer period of time for the in-process material to be taken to the next step. The statement provided by the Site Head contradicts the conclusion drawn during the investigation. Root causes identified in the investigation do not represent the actual reason for the delay in this case.

OBSERVATION 3

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, your (b) (4) hold time studies do not represent those of commercial batches and the quantity used for these studies are not justified. (b) (4) hold time studies of products intended for the US market were performed as per protocol titled, "Hold Time Study Protocol for Compressed or (b) (4) (b) (4) Tablets as Finished Product" (# HT2/004-00). According to protocol HT2/004-00 and other hold time study protocols, irrespective of the batch size, only (b) (4) of the representative (b) (4) sample was stored in a simulated container. For example, the following is a summary of selected samples for the (b) (4) old time study:

Product	Strength	Batch Size	Quantity used for (b) (4) Hold Time Study
(b) (4) Tablets USP	(b) (4) ng/(b) (4) ng/(b) (4) ng	(b) (4)	
(b) (4) Tablets USP	(b) (4) ng (b) (4) ng (b) (4) ng (b) (4) mg		
(b) (4) Tablets USP	(b) (4) ng/(b) (4) ng		

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	5/8/2017-5/19/2017* FEI NUMBER 3007549629

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
TO: Amit Sareen , Site Head and Vice President - Manufacturing

FIRM NAME	STREET ADDRESS
Lupin Limited	Unit 2 - Plot No. 2, SEZ Phase II, Misc., Apparel Park, District Dhar, Pithampur
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Indore, Madhya Pradesh, 454775 India	Drug Manufacturer

(b) (4) Tablets USP	(b) (4) ng/ (b) (4) ng	(b) (4)
(b) (4) Tablets USP	(b) (4) ng	

OBSERVATION 4

The batch production and control records are deficient in that they do not include identification of persons performing, supervising and checking each significant step in the operation.

Specifically, there was no identification of the person entering the values from critical process steps in the batch manufacturing records and there was a lack of second person verification of each step. For example,

- Number of bottles went into incubation in each (b) (4) were entered into the batch manufacturing record (Batch# (b) (4) without anyone signing the page during the aseptic process simulation (Media Fill).
- Visual inspection of incubated bottles for the microbial contamination results were entered into the batch manufacturing records by the analysts without anyone checking or verifying.

OBSERVATION 5

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use.

Specifically, the qualification of your firm's stability chambers lacks data to fully support the temperature uniformity throughout the chambers.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Tamil Arasu, Investigator TA Darren S. Brown, Investigator DB	5/19/2017

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	5/8/2017-5/19/2017* FEI NUMBER 3007549629

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
TO: Amit Sareen , Site Head and Vice President - Manufacturing	
FIRM NAME Lupin Limited	STREET ADDRESS Unit 2 - Plot No. 2, SEZ Phase II, Misc., Apparel Park, District Dhar, Pithampur
CITY, STATE, ZIP CODE, COUNTRY Indore, Madhya Pradesh, 454775 India	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

- The temperature mapping of your firm's stability chambers is based on fixed temperature & humidity probes within the stability chambers. According to the mapping diagrams each stability chamber has a total of (b)(4) temperature & humidity probes which have been permanently installed on the (b)(4) panels of the chambers. Each of the (b)(4) probes has data loggers which record temperature and humidity data at its location. As an example, for stability chamber SC-11, which is kept at 25±2 °C/60±5% RH and has a capacity of (b)(4) L, the firm could only provide temperature and humidity data for each of the fixed probes. This stability chamber is used for long-term stability studies for US products. The firm has not provided temperature & humidity data to show that the temperature and humidity in the center of their stability chambers meets the specified conditions.

OBSERVATION 6

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

Specifically, your firm does not have a procedure in place to verify if the (b)(4) back-up (b)(4) (b)(4) 01) for the (b)(4) Storage Tank (T-602-1) will work. According to SOP EN2-079-03 section 5.4.18 "Operation of (b)(4) Unit and Distribution Loop," your firm's engineering personnel are to "ensure that tank (b)(4) should be maintained NLT (b)(4) by (b)(4) or (b)(4) , (b)(4) 01 is the back-up (b)(4) for the firm's (b)(4) storage tank (T-602-1) in the event that there is an interruption to the (b)(4) supply. Your firm does not regularly verify that the (b)(4) 01) works as intended. This (b)(4) is used for the regular manufacturing of sterile (b)(4) products such as (b)(4) Solution, (b)(4) % and (b)(4) Solution, (b)(4) %.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Tamil Arasu, Investigator TA Darren S. Brown, Investigator DB	5/19/2017

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	5/8/2017-5/19/2017* FEI NUMBER 3007549629

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
TO: Amit Sareen , Site Head and Vice President - Manufacturing

FIRM NAME	STREET ADDRESS
Lupin Limited	Unit 2 - Plot No. 2, SEZ Phase II, Misc., Apparel Park, District Dhar, Pithampur
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Indore, Madhya Pradesh, 454775 India	Drug Manufacturer

***DATES OF INSPECTION**
5/08/2017(Mon),5/09/2017(Tue),5/10/2017(Wed),5/11/2017(Thu),5/12/2017(Fri),5/15/2017(Mon),5/16/2017(Tue),5/17/2017(Wed),5/18/2017(Thu),5/19/2017(Fri)

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Tamil Arasu, Investigator Darren S. Brown, Investigator	5/19/2017