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	3/27/2017-4/7/2017* FEI NUMBER 3004819820

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

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 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, from January 2016 to March 2017, your firm has invalidated several initial Out-of-Specification (OOS) results as summarized below:

Product	No. of OOS Investigations	No. of OOS Investigations Deemed Invalid	% OOS Invalidated
Commercial Finished Product	89	67	75%
Stability	31	30	97%
Raw Material	48	34	71%

(A) OOS Investigation OOS/E/16/GA/SS/125 was initiated (on 09/24/2016) to probe the 1-Month Stability Assay failure for (b) (4) and (b) (4) Tablets, (b) (4) mg /(b) (4) mg, Batch (b) (4). A failing Assay result of (b) (4) % was obtained against a specification limit of (b) (4) % to (b) (4) % for (b) (4) (b) (4) content. You invalidated the initial results through re-testing and reported the average results of replicate retests ((b) (4) %). Evaporated sample solvent was identified as a probable cause of the OOS results. However, you did not take appropriate corrective and preventative actions to ensure that the evaporation of sample solvent, to which you attributed the failure, would not affect other analytical work in your laboratory.

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	Jogy George, Investigator Andrew Idzior, Investigator	04/07/2017

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(B) OOS Investigation OOS/C/16/GA/FP/223 was initiated (on 12/26/2016) to probe the Assay failure of (b) (4) Tablets, USP (b) (4) mg, Batch (b) (4) A failing Assay result of (b) (4) % was obtained against a specification limit of (b) (4) % to (b) (4) % for (b) (4) content. You invalidated the initial results through re-testing and reported the average results of replicate retests (b) (4) %). Evaporated sample solvent was identified as a probable cause of the OOS results. However, you did not take appropriate corrective and preventative actions to ensure that the evaporation of sample solvent, to which you attributed the failure, would not affect other analytical work in your laboratory.

(C) OOS Investigation OOS/I/16/GA/RM/022 was initiated (on 12/26/2016) to probe the Assay failure during API testing of (b) (4) USP, Batch (b) (4) . A failing Assay result of (b) (4) % was obtained against a specification limit of (b) (4) % to (b) (4) %. You invalidated the initial result as an outlier through re-testing and reported the average results of replicate retests (b) (4) %). Your investigation did not reach an assignable cause.

(D) OOS Investigation OOS/E/14/GA/FP/135 was initiated (on 11/22/2014) to probe the Content Uniformity failure for (b) (4) Tablets, (b) mg, Batch (b) (4) . Failing Content Uniformity results were obtained for Sample No. (b) and (b) (4) yielding (b) (4) % and (b) (4) %, respectively. The investigation concluded that the OOS result was "due to improper rinsing of shaft after (b) (4) of the sample solution No.(b))". The conclusion was assumed and not made on the basis of scientific evaluation. You invalidated the initial results through re-testing. The investigation did not extend to review of the manufacturing process to ascertain if the content uniformity issues were attributed by the manufacturing process. Batch (b) (4) s an exhibit batch filed in support of (b) (4) (b) (4)

(E) OOS Investigation OOS/E/15/GA/FP/003 was initiated (on 01/19/2015) to probe the Content Uniformity failure for (b) (4) Tablets, (b) mg, Batch (b) (4) . Failing Content Uniformity results were obtained from Sample No. (b) and (b) yielding (b) (4) % and (b) (4) %, respectively. The investigation concluded that the OOS is due to "improper rinsing of shaft after (b) (4) of sample solution with respect to sample solution No. (b) (4) . The conclusion was assumed and not made on the basis of scientific evaluation. You invalidated the initial results through re-testing. The investigation

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did not extend to review of the manufacturing process to ascertain if the content uniformity issues were attributed by the manufacturing process. Batch (b) (4) is an exhibit batch filed in support of (b) (4) (b) (4)

(F) Out-of-Trend Investigation OOT/GA/14-027-EB was initiated (on 12/1/2014) to probe the (b) (4) (b) (4) failure for (b) (4) Tablets, (b) mg, Batch (b) (4). (b) (4) (b) (4) result indicating an OOS Acceptance Value, AV = (b) (4) % was generated from Tablets representing the "(b) (4)". The investigation concluded with improper (b) (4) of the sample as probable cause. A review of the manufacturing process was not conducted particularly when the same batch indicated an increasing trend in the variability (b) (4) (b) (4) in (b) (4) during the (b) (4) activity. The investigation did not consider the in-batch OOT (b) (4) variation to be potentially related to the manufacturing process. Batch (b) (4) is an exhibit batch filed in support of (b) (4)

(G) OOS Investigation OOS/I/17/GA/RM/015 was initiated (on 01/30/2017) to probe the API Particle Size testing of (b) (4), USP, Batch (b) (4) The particle size testing yielded results as follows:

(b) (4) (b) (4) microns [Specification: < (b) (4) microns]
microns [Specification: (b) (4) to (b) (4) microns] – Failing Results
microns [Specification: > (b) (4) microns]

You invalidated the initial results without adequate investigation, performed re-testing using new samples, and reported the average results of replicate re-tests. You stated in your investigation report that the OOS "may be probably due to (b) (4) or sampling handling". You have not provided conclusive evidence to show that (b) (4) and/or sample handling resulted in the OOS results for (b) (4) The difference between the (b) (4) OOS results and vendor COA [(b) (4) = (b) (4) microns)] for the same API lot is approximately 5 microns. The conclusion was assumed and not made on the basis of scientific evaluation.

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(H) You have not provided training for laboratory analysts in a consistent manner for investigations that are purportedly caused due to laboratory and/or analyst error. In addition, you do not have a robust system to ensure that the trainings that you provide are adequate and effective. The number of analysts that received training varies, does not included all analysts, and re-training requirement is not well defined. Few examples are listed below;

Product	OOS No./ Date of Occurrence	Test	Resp. Analyst	Total Analysts Trained	Training Date	Comments
(b) (4) Tablets, USP (b) (4) mg	OOS/C/15/GA /FP/016 (01/16/15)	Dissolution	(b) (6)	(b) (4)	02/04/15	Training not imparted to 100% of laboratory analysts
(b) (4) Tablets, USP (b) (4) mg	OOS/C/15/GA /FP/360 (12/22/15)	Dissolution	(b) (6)	(b) (4)	12/26/15	Training not imparted to 100% of laboratory analysts
(b) (4) Tablets, USP (b) (4) mg	OOS/C/16/GA /FP/034 (02/12/16)	Dissolution	(b) (6)	(b) (4)	02/20/16	Repeat error made by same analyst. Effectiveness of training not evaluated.
(b) (4) (b) (4) Tablets, (b) mg	OOS/E/14/GA/ FP/135 (11/22/14)	Content Uniformity	(b) (6)	(b) (4) (including analyst: (b) (6))	12/23/14	Training not imparted to 100% of laboratory analysts
(b) (4) (b) (4) Tablets, (b) mg	OOS/E/15/GA/ FP/003 (01/19/15)	Content Uniformity	(b) (6)	(b) (4)	03/14/15	Repeat error made by re-trained analyst (b) (6) Effectiveness of training not evaluated

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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,

(A) The (b) (4) Hold Time studies that you have conducted for products marketed in the US are deficient. The batch sizes used for the establishment of (b) (4) Hold time do not represent the commercial batch size of the products. Hold time studies at the (b) (4) stage were conducted utilizing previous versions of SOP No: SAP-079-09. The prior versions of the same SOP required a representative (b) (4) sample to be collected (b) (4) the (b) (4) stage and the sample was stored in simulated containers. The (b) (4) stage sample quantity requirement was (b) (4) regardless of the batch size. To date, you have conducted (b) (4) hold time studies utilizing this approach for (b) (4) representing approximately (b) (4) products intended for the US market. Examples listed below include products manufactured either by (b) (4) process and/or with relatively low amount of active content with their respective hold time study summary (b) (4) Stage).

Product	Batch Size (b) (4) Stage)	Quantity used for (b) (4) Hold Time Study	Established Hold Time (b) (4) Stage)
(b) (4) TABLETS USP (b) (4) MG	(b) (4)	(b) (4)	(b) (4)
(b) (4) TABLETS USP (b) (4) MG			
(b) (4) TABLETS (b) MG			
(b) (4) SUSP (b) (4) MG/(b) ML USP			

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(b) (4) TABLETS USP (b) mg	(b) (4)	(b) (4)	(b) (4)
(b) (4) TABLETS USP (b) (4) MG			
(b) (4) CAPSULES USP (b) (4) MG			
(b) (4) & (b) (4) TABLETS (b) (4) MG (b) (4) MG			
(b) (4) TABLETS USP (b) (4) MG			

Since January 2015, approximately 20 investigations have been initiated for either (b) (4) or Assay failures at the (b) (4) Stage for products marketed in the US. The current version of SOP No: SAP-079-09 (effective: 7/19/2016) requires the (b) (4) batch size to be held for study purpose. You have not conducted any retrospective evaluation of the need to repeat (b) (4) Hold time studies.

(B) The Process Validation of (b) (4) Tablets, (b) (4) mg is potentially deficient. Process Validation batch (b) (4) was compressed on (b) (4) Compression Machine with equipment ID: PR-TCM-002. The documented qualification speed range (as per VP/OQ/151, effective 04/26/2005) for this compression machine is (b) (4) RPM to (b) (4) RPM. However, the aforementioned Process Validation Batch (b) (4) was compressed at a speed of (b) (4) RPM. Additionally, compression speed studies were conducted as part of pre-validation studies. Therein, the (b) (4) Speed studies were conducted at a compression speed of (b) RPM. The (b) RPM speed was found to be below the range of (b) (4) speed calibration limits (b) (4) to (b) (4) RPM) dated 03/09/2017. Additional review revealed that you have a number of other products for which the Master Batch Manufacturing Record include speed ranges that are outside the documented qualification speed range (b) (4) to (b) (4) RPM) of the Tablet Press. Your firm lacks procedural controls to ensure that proposed speed ranges in the Master BMR is commensurate with the qualified parameters of critical production equipment. Examples are listed below:

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Product	Batch Size	Master BMR Compression Machine Speed Range**
(b) (4) Tablets (b) (4) mg	(b) (4) Tablets	(b) (4) to (b) (4) RPM
Tablets mg	(b) (4) Tablets	(b) (4) to (b) (4) RPM
Tablets mg	Tablets	(b) (4) to (b) (4) RPM
(b) (4) Tablets USP (b) (4) mg	Tablets	(b) (4) to (b) (4) RPM
Tablets USP mg	(b) (4) Tablets	(b) (4) to (b) (4) RPM
(b) (4) Tablets USP (b) mg	Tablets	(b) (4) to (b) (4) RPM
(b) (4) Tablets (b) (4) mg	Tablets	(b) to (b) (4) RPM
(b) (4) Tablets mg	Tablets	(b) (4) to (b) (4) RPM
(b) (4) Tablets (b) (4) mg	Tablets	(b) (4) to (b) (4) RPM
(b) (4) Tablets (b) mg	Tablets	(b) (4) to (b) (4) RPM
(b) (4) & (b) (4) Tablets (b) mg/ (b) (4) mg	Tablets	(b) (4) to (b) (4) RPM
(b) (4) & (b) (4) Tablets (b) mg/ (b) (4) mg	Tablets	(b) (4) to (b) (4) RPM

** Qualified Compression Machine Speed Range: (b) (4) to (b) (4) RPM for Equipment ID: PR-TCM-002

OBSERVATION 3

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, your firm utilizes (b) (4) Testers during in-process (b) (4) testing of all tablet products intended for the US market. In-process tests such as Weight, (b) (4) (b) (4) etc. are electronically recorded using the SCADA system. The (b) (4) tester includes a "Reset" button that can be potentially used to terminate a test run before it is completed. This was verified during the facility walkthrough on 03/31/2017 during the (b) (4) of a product intended for the US market ((b) (4) Tablets, USP (b) (4) mg). The operators were asked to press the "Reset" button during a (b) (4) test of n=(b) (4) tablets. The SCADA system did not log the Reset event and no printout

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was recorded for the partially completed test. You do not have any procedural controls to ensure all (b) (4) testing events (particularly the partially completed tests or aborted tests) are recorded by the SCADA system. The following is a summary of (b) (4) testers utilized at your facility during routine commercial manufacturing of products intended for the US market:

Production Area	Equipment ID No.	No. of (b) (4) Testers
(b) (4)		

***DATES OF INSPECTION**
3/27/2017(Mon),3/28/2017(Tue),3/29/2017(Wed),3/30/2017(Thu),3/31/2017(Fri),4/03/2017(Mon),4/04/2017(Tue),4/05/2017(Wed),4/06/2017(Thu),4/07/2017(Fri)

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