Inspections, Compliance, Enforcement, and Criminal Investigations

Lupin Limited 5/7/09

Department of Health and Human Services

Public Health Service
Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH

Office of Compliance
International Compliance Team
10903 New Hampshire Avenue,
WO Bldg 51
Silver Spring, MD 20993

Warning Letter

Via FedEx

WL: 320-09-05

May 7, 2009

Dr. Desh Bandhu Gupta
Chairman
Lupin Limited
Plot No. C-25, Laxmi Towers
"G" Block, "C" Wing, 4th Floor, Bandra Kurla Complex
Bandra (East) Mumbai, India 400 051

Dear Dr. Gupta,

This is regarding an inspection of your sterile and non-sterile pharmaceutical manufacturing and sterile active pharmaceutical manufacturing facility (Mandideep), in Bhopal, India by Investigator Michael R. Goga and Microbiologist Parul M. Patel during the period of October 31 - November 12, 2008. The inspection revealed significant deviations from U.S. current good manufacturing practice (CGMP) regulations (Title 21, Code of Federal Regulations, Parts 210 and 211) in the manufacture of finished drug products.

These deviations were listed on an Inspectional Observations (Form FDA 483)

issued to Vilas S. Satpute, Senior Vice President, API Manufacturing and Site Head at the close of the inspection. These CGMP deviations cause the drug products and APIs to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act), [21 U.S.C. § 351(a)(2)(b)]. Section 501(a)(2)(B) of the Act states that drugs are adulterated when they are not manufactured, processed, packed, and held according to current good manufacturing practices. Failure to comply with CGMP constitutes a failure to comply with the requirements of the Act.

We have received your December 9, 2008, January 13, 2009, February 12, 2009, and March 10, 2009 written responses to the FDA-483 observations. We acknowledge that some corrections appear to have been completed or will soon be implemented. However, your responses do not adequately address some of the deficiencies. Specific violations include, but are not limited to:

1. Failure to maintain production, control, or distribution records associated with a batch of drug product for at least 1 year after the expiration date of the batch. [21 CFR 211.180(a)]

> A. Numerous boxes were observed containing production, control, or distribution records in the destruction area of a separate building (Plant [(b)(4)]). For example, one of these boxes contained a Batch Packing Record (BPR) for Ceftriaxone for Injection USP lOg, Batch Number [(b)(4)], dated August 25, 2008 and August 26, 2008 was awaiting destruction as observed by Investigator Goga. Refer to FDA Form 483, Observation #2.

Your Quality Corporate Management explained during the inspection that Plant [(b)(4)] had no involvement with the Mandideep drug production facility in any way. Yet when our inspection team visited Plant [(b)(4)], they observed 20 boxes containing documents and files from the Mandideep Plant [(b)(4)] facility. Please explain the discrepancy in the information given by your Quality Management to our investigators.

You state in your December response that the documents seen by our investigators during the inspection, and referred in Form FDA 483, Observation #2, were either expired or outside the specified retention time period specified in your document retention policy. In addition, you explained to our inspection team that the 20 boxes of documents stored in Plant [(b)(4)] were being held waiting for destruction. Your December response referencing Batch Packing Records (BPRs) from 2006, does not explain why the partial BPR for Ceftriaxone for Injection USP l0g was awaiting destruction. This record falls within the storage period specified in your document retention policy. Your response should provide an explanation regarding your decision to destroy these records.

2. Failure to follow appropriate written procedures designed to prevent microbiological contamination of drug products to be sterile. [21 CFR 211.113(b)]

A. All personnel who enter the aseptic filling area are not monitored. Refer to

FDA Form 483, Observation #7.

Our inspection team reviewed documents of individuals entering and exiting the aseptic fill area. Personnel such as maintenance, cleaning, supervisors, and operators (i.e.: filling machine operators, [(b)(4)] operators) were not required to follow written procedures that they be microbiologically monitored. Your December response (Attachment 15) is incomplete in that it did not specify the roles of personnel who completed training for the "Environmental Monitoring Procedure - Vial Filling facility" your firm provided. Please provide more detailed information showing the roles of employees such as maintenance, cleaning, and supervisors who completed this training.

3. The controls to prevent contamination in defined (critical) areas are deficient regarding operations related to aseptic processing of products. [21 CFR 211.42(c)(10)]

A. Smoke studies of Class [(b)(4)] in critical areas were inadequate in that they were not performed under dynamic conditions and the results were not recorded for subsequent review. Refer to FDA Form 483, Observation #5.

You included a CD ROM of the smoke study summary report with your December response. However, this CD ROM was unable to be opened for review, thus we could not read the attached documents. Re-submit the supporting documentation including the video showing the smoke study your firm conducted on November 19, 2008.

4. Failure to routinely calibrate, inspect, or check according to a written program designed to assure proper performance of automatic, mechanical, or electronic equipment, including computers, used in the manufacture, processing, packing and holding of a drug product. [21 CFR 211.68]

A. The Enterprise Resource Planning System known as the firm's Systems Applications and Products (SAP) computer database allows rejected batches of drug product to be in Unrestricted Status (to be released for distribution). Refer to Form FDA 483, Observation #3.

Please provide additional information to support that your current Enterprise Resource Planning SAP system provides limited access to only "approved QA personnel" versus warehouse or production personnel. Your December response states any correction or change in Usage Decision (UD) will require next-level QA authorization in SAP. Explain how you are able to ensure that only QA authorized personnel are changing the status of the lots in the SAP system, and how it is documented and/or tracked.

In addition, your December response in Attachment #4, "Performance Qualification Report for SAP R/3 Enhancement", shows lots that can be "Partially Approved" without selecting a Usage Decision. Provide an explanation as to what "Partially Approved" is defined as, who has the authority to make this decision, how it is documented, and why this status is "not applicable" in

the Usage Decision status.

B. Failure to retain original calibration data for [(b)(4)] used in the re-qualification of the [(b)(4)]. Refer to Form FDA 483, Observation #4b.

During the inspection, you provided our FDA investigators a spreadsheet that you stated contained data for calibration of [(b)(4)], however, you were not able to provide the raw calibration data. In addition, the calibration data for the [(b)(4)] that you provided in your December response in Attachment #9 do not correspond to the [(b)(4)] observed by our FDA investigators. The [(b)(4)] observed during our inspection had a different manufacturer, tag number, and temperature range than the [(b)(4)] for which you provided data in your response. Please explain this discrepancy.

C. Written records of calibration were not adequately verified. Refer to Form FDA 483, Observation #9.

The inspection team was shown internal calibration certificates for [(b)(4)] that were performed at readings of [(b)(4)], yet the raw data does not document these readings. This data was verified and signed by a second individual and calibration certificates were generated. In addition, the calibration of a [(b)(4)] shows incorrect entries on the Instrument Calibration record. Yet this record was also verified and signed by a second individual. Your response do not show that investigations were conducted. Please provide the investigation reports.

Your December response states all data is now concurrently verified by immediate supervisors, however this is not stated in your attached, revised procedure, "[(b)(4)], Calibration of Instruments." In addition, you stated in your response that calibration records will be routinely reviewed by QA. Provide the relevant written procedure(s) to reflect this review is conducted.

5. Failure to follow written procedures describing the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures. [21 CFR 211.80(d)]

A. Approximately [(b)(4)] bulk empty glass vials were not labeled with any identification such as an item code, material code, SAP code, lot number or acceptance status. These vials were located in a separate building - Plant [(b)(4)] Refer to Form 483, Observation #1.

Your December response stated that these vials were segregated due to minor cosmetic defects and were labeled with an item code. Yet the inspection team reported that they did not observe any type of identification on the vials or the containers. Please explain how you determined which vials were destined for the Indian market without an item code. Include an explanation of the [(b)(4)] vials [(b)(4)] Type ([(b)(4)]) that were "approved" that were stored in Plant [(b)(4)]. Please provide supporting documentation showing that the defective vials were dest1byed as stated in your written response. Your December

response states that the [(b)(4)] vials had been stored in Plant [(b)(4)] due to storage space constraints in the main warehouse. Your responses do not address whether you will continue to use Plant [(b)(4)] to store drug components, including drug containers and closures.

6. Documentation of each significant step in the manufacture, processing, packing or holding of the batch was not performed by the persons performing each significant step in the operation. [21 CFR 211.188(b)(11)]

A. The batch production records for the system simulation (Batch#: [(b)(4)]), do not document the results by the individual who performed the actual visual inspection of the media fill vials in Phase [(b)(4)]. Refer to FDA Form 483, Observation #6.

Your written responses state Quality Assurance (QA) is now responsible for recording the observations of the media fills. Please provide further details on the microbiological qualifications and GMP training of the QA personnel who will be recording the media fill results.

7. Failure to maintain buildings in a clean and sanitary condition used in the manufacture, processing, packing, or holding of a drug product. [21 CFR 211.56(a)]

A. The inspection team observed a collection of water with black residue in the surrounding area underneath and in the area adjacent to the [(b)(4)]. Refer to FDA Form 483, Observation #12

Your responses did not address the investigation conducted or the identification of the black residue. Provide in your response the investigation report with your findings including the cleaning methods you performed. Please provide the location of this sampling port and the equipment surrounding it. Also, explain if any drug processing, holding, or repackaging is conducted in this area.

In addition, the inspection team observed an accumulation of water on the floor in the [(b)(4)] treatment plant which can become a source of [(b)(4)] contamination. A greenish film was observed in the bottom of the water drain channel in the [(b)(4)] plant. Refer to Form FDA 483, Observation #8.

Your responses did not address if an investigation was conducted or confirmation that the green color on the bottom of the drain was identified as paint or if it was biofilm. Provide the investigation report and supporting documentation.

8. Failure to investigate the failure of a batch or any of its components to meet any of its specifications. A written record of the investigation shall be made and shall include the conclusions and follow-up. [21 CFR 211.192]

A. The QA monthly report dated 01 JAN 08 included one finished product

sample that failed, however there is no record that an Out-of Specification investigation was performed. Refer to Form FDA 483 Observation #13.

You explained in your December response that the OOS reported in the January 2008 Monthly Quality Report was a typographical error. Please provide the documentation for the investigation you performed to make this conclusion.

Please provide further explanation regarding your position that QA monthly reports are not subject to GMP requirements, given that the reports include information such as testing summary, Out of Specification results, audits, complaints, and changes implemented. At the end of the inspection. you explained to our inspection team that the QA monthly reports were considered [(b)(4)] reports and not GMP documents. We have reviewed the information collected and agree with our inspection team that the QA monthly reports are subject to GMP requirements. Your December response to Form FDA 483, Observation #13 states the monthly report "is used as a management tool only." In addition, your response states this document is prepared and issued to your Corporate Management to apprise them of potential adverse quality trends.

GENERAL COMMENTS:

Regarding your written responses to FDA Observation #4:
In your December response, Attachment #7 describes the Performance Qualification (PQ) Validation Plan for the [(b)(4)] Mapping Plan of the [(b)(4)]. The validation plan of the [(b)(4)] describes [(b)(4)] studies, however does not include any [(b)(4)] Test (single run for l0ml vial). Since the [(b)(4)] is used for [(b)(4)] provide the justification as to why an [(b)(4)] test was not performed as part of your PQ. In addition, for other size vials shipped to the U.S. market, explain the justification to perform your PQ using a single run for the l0ml vial.

In addition, your firm stated in your responses that you compared the [(b)(4)] logger data obtained using your new data logger with the data from the earlier qualification reports and found the new and old data to be comparable (Attachment #8). Provide an explanation with supporting documentation as to the actual raw data generated from the older data loggers used in the earlier qualification reports and how you compared the older data with the data from the new data logger.

Regarding other documents observed in Plant [(b)(4)]:

The [(b)(4)] logbooks 2006-2007 and Operational Log for Air Handling Unit 2007 are documents that pertain to equipment usage. Your December response states that these documents were not required to be retained by the previous record retention policy. These logbooks maintain information relating to system functioning, prior, during, and after the manufacture of drug products, and need to be retained. Please provide further explanation as to the reason for their planned destruction and which other production-related documents are destroyed under this policy.

There were additional files observed in different locations of Plant [(b)(4)], referred as "corridor boxes", but not mentioned in the FDA Form 483 such as Daily Observation and Complaint file, Raw Data Cleaning Validation, Environmental Monitoring Record for the year 2006, [(b)(4)] Analysis Reports, Manufacturing Differential Pressure Monitoring Record, to name a few. When this observation was discussed at the end of the inspection, your management did not provide our investigators information as to the final disposition of these records, or why they were being held at Plant [(b)(4)] for destruction and not Plant [(b)(4)].
Please explain.

The CGMP deviations identified above or on the FDA-483 issued to your firm are not to be considered an all-inclusive list of the deficiencies at your facility. FDA inspections are audits, which are not intended to determine all deviations from CGMPs that exist at a firm. If you wish to continue to ship your finished drug products and APIs to the United States, it is the responsibility of your firm to assure compliance with all U.S. standards for current good manufacturing practices.

Until all corrections have been completed and FDA can confirm your firm's compliance with CGMP, this office will recommend disapproval of any new applications or supplements listing your firm as a manufacturing location of finished dosage forms and APIs. In addition, shipments of articles manufactured by your firm are subject to refusal of admission pursuant to Section 801(a)(3) of the Act in that the methods and controls used in their manufacture do not appear to conform to Current Good Manufacturing Practice within the meaning of Section 501(a)(2)(B) of the Act.

Please respond to this letter with requested documents translated in English within 30 days of receipt and identify your response with FEI# 3002807511. Please contact Yumi Hiramine, Compliance Officer, at the telephone number shown below, if you have any questions or concerns regarding this letter.

U.S. Food & Drug Administration
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International Compliance Branch
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To schedule a re-inspection of your facility, after corrections have been completed and your firm is in compliance with cGMP requirements, send your request to: Director, Division of Field Investigations HFC- 130, 5600 Fisher's Lane, Rockville, MD 20857. You can also contact that office by telephone at (301) 827-5655 or by fax at (301) 443-6919.

Sincerely,

/s/

Richard L. Friedman
Director
Division of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research