U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Inspections, Compliance, Enforcement, and Criminal Investigations

Sun Pharmaceutical Industries Limited - Karkhadi 5/7/14

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

Warning Letter

WL: 320-14-08

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

May 7, 2014

Mr. Subramanian Kalyanasundaram
Chief Executive Officer
Sun Pharmaceutical Industries Limited
Acme Plaza
Andheri - Kurla Rd
Andheri (E)
Mumbai - 400 059
India

Dear Mr. Subramanian Kalyanasundaram:

During our November 13 through November 16, 2013, inspection of your pharmaceutical manufacturing facility, Sun Pharmaceutical Industries Limited - Karkhadi located at Plot No. 817/A, Village, Karkhadi, Taluka, Padra District, Vadodara, Gujarat, India, investigators from the U.S. Food and Drug Administration (FDA) identified violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211, and deviations from current good manufacturing practice (CGMP) for the manufacture of active pharmaceutical ingredients (APIs). These violations and deviations cause your 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), in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have conducted a detailed review of your firm's initial response and note that it lacks sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondence dated January 28 2014, and March 11, 2014.

Our investigators observed specific deviations during the inspection of the API manufacturing facility, including, but not limited to, the following:

1. Failure to ensure that laboratory records included complete data derived from all tests necessary to ensure compliance with established specifications and standards.

For example,

a. Your firm is missing the fundamental raw data and information necessary to document your analyses. For example, these analyses lack the following critical data:

- identification of the samples tested, including name and source, batch number or other distinctive code, and date of the sample
- the complete record of all raw data generated during each test, including graphs and electronic files from laboratory instrumentation

- test method used
- sample preparation as prescribed by the method, preparation and testing of standards, reagents and standard solutions
- records of all calculations performed in connection with the test
- test results
- the signature of the person who performed each test and the date(s) the tests were performed, and the date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with prescribed acceptance criteria

This basic analytical information allows for documentation, review, authentication, traceability, quality control and quality assurance at your pharmaceutical firm.

In addition, minimum laboratory control also includes documenting and retaining your system suitability data.

b. Your firm frequently performs "unofficial testing" of samples, disregards the results, and reports results from additional tests. For example, during stability testing, your firm tested a batch sample six times and subsequently deleted this data.

Our investigators found your practice of performing initial "trial" sample high performance liquid chromatography (HPLC) analyses prior to acquiring the "official" analyses. The "trial" sample results were subsequently discarded. "Trial" HPLC analyses for **(b)(4)** USP (**(b)(4)**) were apparently run as part of the 12-month long-term stability studies on batch #**(b)(4)** for related substances. The inspection revealed tha on August 26, 2011, your employee ran an HPLC analysis sequence with the sample names **(b)(4)** and subsequently deleted the raw data files. It was noted that the assigned names for the sequence injections indicates that your quality control staff named the samples using the last three digits of the batch numbers to link the "trial" injections for the batches with the official assay analyses. Your Senior Quality Control (QC) Officer confirmed that these were analyses of batch samples. Furthermore, we found that on August 27, 2011, this batch was analyzed for unknown impurities and the results were reported to be within specifications. However, the chromatographic data showed that the "trial" injection data for this batch failed the unknown impurities specification of **(b)(4)**% in multiple cases.

Your Senior QC Officer confirmed that QC laboratory employees had frequently practiced the use of "trial" injections at your facility. Significantly, in addition to the example above, our inspection found 5,301 deleted chromatograms on a computer used to operate two HLPC instruments in your QC laboratory. Many of these files were "trial" injections of batches.

c. Similar unacceptable data handling practices were observed in your laboratory's conduct of gas chromatography (GC) analyses. The FDA investigators reviewed what appear to be data from "unofficial" injections for GC analyses for recovered **(b)(4)** raw material batch #**(b)(4)**. On February 11, 2012, your analyst performed testing on recovered **(b)(4)** raw material batch #**(b)(4)** and the sample was within specifications. The following day, February 12, 2012, your analyst ran a GC analysis sequence with the sample names **(b)(4)** and subsequently deleted the raw data files. Your staff performed calculations during the inspection, at our request, that showed that these samples did not meet the **(b)(4)** impurity specification for this material. Therefore, it appears that out-of-specification data for batch #**(b)(4)** was considered to be "unofficial," while passing data were reported as the "official" results for the batch.

In addition, the inspection revealed numerous examples of deleted GC electronic raw data files on the computer controlling the GC instruments that were replaced with identical "official" chromatogram file names. The identically named GC data files that were deleted had been created at different times and contained disparate data. Also, it appeared that data was not consistently archived to the central server.

Your response is inadequate in that you did not conduct an adequate investigation into the pervasive practice of deleting files. In the reports provided in your response, you did not identify what criteria you used to designate each type of HPLC and GC data files (e.g. blanks, standards, samples, and system suitability runs). The response does not identify any impurity standards used in your procedures and does not provide the procedures that your firm was using to conduct the "trial" and "unofficial" runs. In addition your investigation found 47 instances of apparent trial injections of samples for which the results were out-of–specification (OOS), and some of these batches were distributed to the U.S. market. The investigation failed to adequately examine why your analysts hid or deleted these runs. Your response only explains that your firm chose to retest samples from the implicated lots, but does not address the causes o the original OOS results, or justify the basis of your decision to invalidate the original failing result and accept the passing retest result. Such an investigation is necessary for any OOS event. Refer to the FDA's guidance on OOS investigations *Guidance for Industry, Investigating Out-of-Specification (OOS), Test Results for Pharmaceutical Production.*

The above examples suggest a general lack of reliability and accuracy of data generated by your firm's laboratory, which is a serious CGMP deficiency that raises concerns about the integrity of all data generated by your firm. We are concerned that your laboratory allowed the practice of "trial" injections and deletion of both GC and HPLC files to persist without implementation of controls to prevent data manipulation until at least September 2013. Your company's executive management is responsible for ensuring the quality, safety, and integrity of your products. Implementing adequate controls and systems to prevent manipulation of laboratory data is at the foundation of fulfilling this critical responsibility.

2. Failure to assign and identify raw materials with a distinctive code, batch, or receipt number, and to identify the disposition of materials.

For example,

a. The investigators observed three partially filled unidentified bags of **(b)(4)** in your firm's raw materia warehouse. Your employees were unable to determine conclusively the identity or status of the material.

b. The investigators observed numerous unidentified partially filled bags containing what appeared to be **(b)(4)** in the **(b)(4)** Room. The disposition of this unlabeled material was not clear at the time of the inspection.

It is essential that employees adequately label materials as to their identity and status to prevent mix-ups and their unintentional or unauthorized use. In your response, you commit to amend your materials management system to ensure that your employees maintain accurate and adequate labeling of all materials. In response to this letter, provide evidence that you have implemented these corrective actions. Also, include your training activities for relevant personnel (e.g., staff, managers) to ensure adequate material handling.

Our investigators also observed significant violations regarding the finished drug product manufacturing operations at your facility, including, but not limited to, the following:

1. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

The investigator identified numerous deleted raw data files on computers used for your GC instruments in your quality control laboratory. The software ("GC Solutions") on the computers used to control the GC instruments allowed your analysts to delete files from the computer's hard drive with no audit trail or othe adequate form of traceability in the operating system to document the deletion activity. The software as configured assigned sequential, numerical names to raw data files within the same folder. When a raw data file was deleted or moved out of the designated folder, the next file recorded into the folder would be saved with an identical name as the deleted file. As a result, data can be manipulated so that saved files appear to be in sequence even if they were not generated sequentially. Due to the basic lack of audit trail and data security, an analyst could delete analytical files without traceability of this unacceptable practice.

The inspection revealed that you stored GC raw data files in multiple folders on the hard drives in the QC laboratory. Your Senior QC Officer stated you had no written procedure describing the management of GC raw data file storage. According to your firm's electronic data archival SOP IT-001, each QC analyst manually transferred individual raw data files to the central server at **(b)(4)**. Your procedure did not address how this data transfer by QC analysts could be reliably verified, and whether proper computerized system controls will be implemented by your company.

We acknowledge your firm's commitment to amend the data handling system of your GC instruments to implement controls that ensure that analyses performed by employees are maintained as accurate, with data integrity and traceability. In your response to this letter, describe your detailed systemic improvements, training activities, and other actions implemented to provide evidence of the effectiveness and sustainability of these changes.

2. Your firm failed to maintain written production, control, or distribution records specifically associated with a batch of a drug product for at least one year after the expiration date of the batch (21 CFR 211.180(a)).

During the inspection, the investigators found approximately 10 waste bags containing torn or partially destroyed raw data CGMP records related to a variety of manufacturing activities. Some of the records found in these waste bags included the following:

a. A calibration check record for balance #FI-002 was torn and partially destroyed. Your associate stated

that he used the wrong weights when conducting the calibration. He said that he recalibrated the balance and prepared new documentation, and subsequently discarded the original record. Furthermore, we learne that additional original calibration records of other balances had similarly been discarded.

b. Six corrective action and preventive action (CAPA) records (form F03-QA-076/01) were torn. Your Senior Quality Assurance (QA) Officer stated that this form is used for extending the due date of an ongoing CAPA. Our inspection team compared the discarded records to the official records and identified corresponding official copies of only three of the records. The three other discarded records did not have ar official corresponding copy. During the inspection, your firm could not produce official records of the corrective actions described in these three partially destroyed documents.

c. Five completed preventive maintenance forms were torn. A staff member stated that he mistakenly tore and destroyed these original records.

The destruction of CGMP records produced by your firm's manufacturing facility is a serious deficiency that raises concerns about the integrity of all records generated by your firm. There was a lack of basic oversight by operations, quality unit, and site managers, as rewriting and destruction of original CGMP records was allowed to persist over a significant period without implementation of systems and controls to prevent data manipulation.

Your response is inadequate in that your investigation was primarily limited to the discarded CGMP records cited in the Form FDA-483. The investigation did not include a comprehensive review of all records in the waste area or a thorough review of your firm's practice of destroying CGMP records. In response to this letter, submit your third party auditor's report of the investigation of the data integrity practices associated with your CGMP records. This report should include a list of all records that your employees rewrote, destroyed, or altered in any way. In addition, address the root cause of your firm's failure to control and detect the manipulation, alteration, or premature destruction of CGMP records and describe systemic actions to prevent recurrence. Provide your procedures to manage and retain all CGMP records.

Also provide a list of all the batches of drug products shipped to the U.S. market and APIs intended for use in drugs to be distributed within the U.S. that relied upon missing, inaccurate, or unreliable records.

3. Your firm failed to ensure that each person engaged in the manufacture, processing, packing, or holding of a drug product has the education, training, and experience, or any combination thereof, to enable that person to perform his or her assigned functions (21 CFR 211.25(a)).

For example, you did not train your contract employees in CGMP or in job-specific procedures. In addition, CGMP documents, including procedures and batch records, apparently could not be fully comprehended by many of the contract employees. Your contract employees conducted critical CGMP operations for your finished drug products such as visual inspection of filled capsules, **(b)(4)** sealing, 100% verification of sealed bottles, final label quality inspection, outsert pasting on bottle caps, and the final packing in boxes. CGMP training is essential to ensure employees are qualified to perform all operations in compliance with good manufacturing practice.

We acknowledge your commitment to amend training procedures for your contract employees to ensure that you adequately train all of them. In response to this letter, provide an update on the implementation of these actions. Also, provide the final investigation report described in your initial response that assesses the deficiencies and their root causes in your training system. Note that only qualified individuals must conduct training. Such training must occur on a continuing basis and with sufficient frequency to ensure that employees remain familiar with CGMP requirements applicable to their assigned functions.

The items listed above, as well as other cited deficiencies, indicate that you have not implemented a robust quality system at your firm. Your corporate management should immediately undertake a comprehensive evaluation of global manufacturing operations to ensure compliance with CGMP regulations. We strongly recommend that you hire a qualified third party auditor with experience in detecting data integrity problems to assist you with this comprehensive evaluation.

You are responsible for the accuracy and integrity of the data generated by your firm. A firm must maintain all raw data generated during each testing and manufacturing operation, including graphs, charts, and spectra from laboratory instrumentation. You must properly identify these records to demonstrate that each released batch was manufactured in accordance with validated parameters, was tested appropriately, and met release specifications.

Appropriate record retention policies should also be in place. Our inspection revealed that your firm destroyed CGMP records directly related to the testing and manufacturing of your products. Your firm should reevaluate your record retention policy for all of your CGMP records. Should product quality or safety concerns arise over the lifecycle of an application, the original records pertaining to batches listed in

an application may be integral in providing reasonable assurances to the Agency regarding a product and integrity of data submitted to support it. When destruction of documents is appropriate, you should follow a documented destruction procedure that ensures documents are destroyed in a controlled manner. This would include, at a minimum, identification of the appropriate documents and retention timelines, documentation of what was destroyed, and the names and signatures of those who witnessed the destruction.

Your data integrity consultant should:

1. Identify any historical period(s) during which inaccurate data reporting occurred at your facilities.

2. Identify and interview your current employees who were employed prior to, during, or immediately after the relevant period(s) to identify activities, systems, procedures, and management behaviors that may have resulted in or contributed to inaccurate data reporting.

3. Identify former employees who departed prior to, during, or after the relevant periods and make diligent efforts to interview them to determine whether they possess any relevant information regarding any inaccurate data reporting.

4. Determine whether other evidence supports the information gathered during the interviews, and determine whether additional facilities were involved in or affected by inaccurate data reporting.

5. Use organizational charts and SOPs to identify the specific managers in place when the inaccurate dat reporting was occurring and determine the extent of top and middle management involvement in, or awareness of, data manipulation.

6. Determine whether any individual managers are still in a position to influence data integrity with respect to CGMP requirements or data submitted to the agency.

7. Expand your internal review to any other facilities determined to be involved in, or affected by, inaccurate data reporting.

8. Include a report that describes in detail the criteria used to determine the identity of the data files generated from the testing of batch, standard, or system suitability samples. The report should include examples of the use of these criteria, as well as identify which data files are standards and samples. In addition, include the procedures followed to prepare samples for system suitability runs (i.e., procedures followed to spike impurities into samples), and to handle product samples and the data files. This assessment should be conducted for both GC and HPLC data.

9. As part of this comprehensive data integrity audit of your laboratory, your audit report also should include any discrepancies between data or information identified in approved applications, and the actual results, methods, or testing conditions submitted to the Agency. Include an explanation of the impact of all discrepancies. Provide a corrective action plan describing the specific procedures, actions, and controls that your firm will implement to ensure integrity of the data in the future. This should cover method validation and any test data (e.g., stability tests, release tests) you have obtained.

The violations and deviations cited in this letter are not intended to be an all-inclusive list of violations and deviations that exist at your facility. You are responsible for investigating and determining the causes of the violations and deviations identified above and for preventing their recurrence and the occurrence of other violations and deviations.

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that coul reduce the number of finished drug products or active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Program immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov so that we can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Program also allows you to meet any obligations you may have to report discontinuances in the manufacture of your drug under 21 U.S.C. 356C(a)(1), and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products. In appropriate cases, you may be able to take corrective action without interrupting supply, or to shorten any interruption, thereby avoiding or limiting drug shortages.

Until all corrections have been completed and FDA has confirmed corrections of the violations and deviations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product or an API manufacturer. In addition, your failure to correc these violations and deviations may result in FDA continuing to refuse admission of articles manufactured at Sun Pharmaceutical Industries Limited - Karkhadi located at Plot No. 817/A, Village, Karkhadi, Taluka,

Padra District, Vadodara, Gujarat, India into the United States under Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3). The articles may be subject to refusal of admission pursuant to Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3), in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of Section 501(a)(2)(B) of the Act, 21 U.S.C. 351(a)(2)(B).

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct and prevent the recurrence of violations, and deviations, and provide copies of supporting documentation. If you cannot complete corrective actions within fifteen working days, state the reason for the delay and the date by which you will have completed the corrections. Additionally, if you no longer manufacture or distribute the drug products and the APIs at issue, provide the dates and reasons you ceased production. Please identify your response with FEI # 3005409363.

Please send your reply to:
Joseph Duran
Compliance Officer
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Manufacturing and Product Quality
International Compliance Branch
White Oak, Building 51, RM 4237
10903 New Hampshire Ave
Silver Spring, MD 20993

Sincerely,
/S/
Michael Smedley
Deputy Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

cc:
Mr. Mukesh R Patel
Factory Head
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