Inspections, Compliance, Enforcement, and Criminal Investigations

Sun Pharmaceutical Industries Inc 8/25/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054
Telephone: (973) 331-4910

WARNING LETTER

WL: 10-NWJ-1

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

August 25, 2010

Mr. Jitendra Doshi
Board of Directors
Sun Pharmaceutical Industries, Inc.
270 Prospect Plains Road
Cranbury, New Jersey 08512

Dear Mr. Doshi:

During our February 25 - April 28, 2010 inspection of your pharmaceutical manufacturing facility Sun Pharmaceutical Industries, Inc., located at 270 Prospect Plains Road, Cranbury, NJ, investigators from the Food and Drug Administration (FDA) identified significant violations of Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your drug products 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 reviewed your firm's response of May 18, 2010, and note that it lacks sufficient corrective actions.

Specific violations observed during the inspection include, but are not limited, to the following:

1. Your firm does not have adequate written procedures for production and process controls designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess [21 C.F.R. § 211.100(a)].

For example, your firm's process for manufacturing Gernfibrozil Tablets, 600 mg, is not in a state of control and is not capable of producing batches of consistent quality. Tablets in three scale-up validation batches (90076,90077,90092) and three batches (BV90105, BV90111, and BV90112) made subsequent to your initial assessment of process performance, experienced "sticking and picking" defects during compression and packaging. Your firm partially released batches 90076, 90077, 90092, after culling tablets with defects, and held the other three batches. Similar defects were not observed in the two exhibit batches (70001 and 70002) manufactured in March 2007 using Magnesium Stearate supplied by **(b)(4)**. However, the Magnesium Stearate used to manufacture the validation batches and subsequent commercial batches was supplied by **(b)(4).** Your January 27, 2010 initial audit of **(b)(4)** noted significant deficiencies which in part resulted in your change back to as **(b)(4)** your supplier.

In addition, initial validation batches 90031, 90032, and 90033 exhibited out-of-specification (OOS) results for unknown impurities at the six-month and nine-month room temperature stability time points. Furthermore retain samples from fifteen lots, seven of which were from initial validation batches, imploded while stored in your retai

sample room.

Your response states that you will not manufacture Gemfibrozil Tablets, 600 mg, until you investigate the root cause of the impurities and imploding bottles and until you re-evaluate and revalidate the manufacturing process and all analytical methods. Before you resume manufacturing, please provide us the results of your completed investigations and documentation that demonstrates your manufacturing process is reproducible.

We acknowledge that your firm initiated a recall of Gemfibrozil Tablets, 600 mg, on March 31, 2010, and submitted a **(b)(4).** However, your corrective actions are inadequate. Specifically, you failed to also provide you plans to ensure the quality of distributed drug products that you manufactured using **(b)(4)** Magnesium Stearate In addition, you failed to provide your plans to ensure that the ingredient suppliers for all of your drug products are adequately qualified.

2. Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications, whether or not the batch has already been distributed, or extended investigations to other batches of drug product that may have been associated with the specific failure or discrepancy [21 C.F.R. § 211.192]. For example,

> a. Although your firm was aware of imploding bottles of Gemfibrozil Tablets, 600mg, in September 2009, you did not initiate a root-cause investigation or conduct a recall to the retail level until our inspection. The retain samples from fifteen lots of Gemfibrozil Tablets, 600 mg, imploded while in your retain sample room You distributed the lots from March 25, 2009, to June 24, 2009.

Your response is inadequate in that you did not explain why you failed to open an investigation in September 2009, when you first identified the problem. Timely assessment of quality indicators, such as OOS findings and complaints, is essential to detecting and determining the scope of product or process deficiencies. In response to this observation, please also provide the details of the investigation and the suspected root cause.

> b. During release testing, batches 90056 and 90057 of Promethazine Hydrochloride (HCI) Tablets, 25 mg, exhibited OOS water content results of 5.7% and 5.9%, respectively (the specification is **(b)(4)**). The OOS results were invalidated after a retest yielded acceptable results, despite your failure to identify an assignable laboratory cause. Furthermore, you failed to extend the investigation to associated batches. The investigation did not include batch 90058 that was analyzed in conjunction with batches 90056 and 90057 and for which passing results were obtained. Yet your Quality Control Unit (QCU) released lots 90056A, 90057A, and 90058A between May 2009 and June 2009.

Your response states that: 1) **(b)(4)** will review all current OOS investigations to determine their adequacy; 2) you will revise Standard Operating Procedure (SOP) 2.2.43, "Handling Out-of-Specification Results," to be consistent with FDA guidance "Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production;" and 3) you will revise OOS worksheets to ensure consistency with SOP 2.2.43. We cannot evaluate the adequacy of your response because you have not completed the investigation and have not implemented mos of your proposed corrective actions. In your response, please clarify whether review will include investigations from the previous two years and future investigations.

3. Your firm has failed to ensure the responsibilities and procedures applicable to your quality control unit are followed [21 C.F.R. § 211.22(d)]. For example,

> a. The QCU failed to ensure customer complaints were adequately investigated as required by SOP 1.1.16, "Quality Unit," dated November 12, 2007. Between August 27, 2008, and December 16,2009, you received fourteen complaints of leaking capsules for multiple lots of Nimodipine Capsules, 30 mg. Your "Corrective Action Summary for Nimodipine Capsules, 30 mg," signed by the Quality Assurance Manager on October 8, 2009, states your firm and your contract manufacturer, **(b)(4)** thoroughly investigated the complaints. Th investigation determined that the potency results for the leaking capsules met specifications. However, your November 11-12, 2009 audit of **(b)(4)** concluded that **(b)(4)** failed to properly determine the impac of product efficacy. Your corrective action summary also identifies the root cause of the leaking capsules and describes the changes made to the formulation, capsule shell, capsule fill weight, and equipment processing parameters based on "small scale experiments." Your QCU approved these changes without verifying the revalidation of the affected manufacturing processes to ensure that the changes were effective and did not adversely affect the drug product.

Your response states you will revise your Quality Agreement with to **(b)(4)** clarify how you will handle investigations and you consider your "enhanced process" to be validated. Your response is inadequate because you failed to provide documentation to support your conclusion that the process is validated. You also failed to provide scientific justification for allowing Nimodipine Capsule lots made prior to the changes to remain on the market.

> b. Your QCU failed to adequately review production and control records to ensure no errors occurred, as required by your SOP 1.1.16. Our investigators noted a discrepancy in the analytical records related to the finished product testing of lot 90056, Promethazine HCI Tablets, 25 mg. The analytical records indicate that you tested lot 80056, rather than lot 90056, for assay. Yet your QCU approved and released lot 90056 without noting the discrepancy.

Your response states that analyst transcription error caused the discrepancy and that the lot was properly assayed prior to release. You state that your firm initiated investigation IR 10-006 to determine why the transcription erro

was not identified prior to release and the appropriate corrective and preventative action plan. However, we cannot determine the adequacy of your response because you failed to provide us with your completed investigation, IR 10-006.

c. Your QCU failed to follow SOP 1.1.14, "Product Recall Procedure," dated May 26, 2006, by failing to notif the FDA when you recalled multiple lots of Gemfibrozil Tablets, 600 mg, on October 23, 2009 from your distributor **(b)(4)**.

Your response states that although you consider **(b)(4)** warehouse an extension of Sun's warehouse, an SOP will be created to define the control mechanisms for product manufactured at Sun and distributed by **(b)(4)**. We cannot determine the adequacy of your response because you failed to provide any further details which demonstrate that the affected Gemfibrozil lots were not recalled because they hadn't left Sun's direct control.

4. Your firm does not adequately inspect the packaging and labeling facilities immediately before use to assure that all drug products have been removed from the previous operations [21 C.F.R. § 211.130(e)].

For example, on July 14, 2009, you found four Oxycodone HCI Tablets, 5 mg, in the brushes of Packaging Line **(b)(4)** while packaging Oxycodone HCI Tablets, 15 mg, lot 90088A. The 5 mg tablets were from lot 90087A whic was packaged on line **(b)(4)** between July 7 and 10, 2009. Although you cleaned and inspected the line before packaging lot 90088A, you failed to detect the 5 mg tablets from lot 90087A. In addition, your investigation, IR 09-106, failed to determine the adequacy of your line clearance procedures and the need for improvements.

Your response states that you consider a line clearance failure to be a critical issue and that you are drafting a ne SOP to ensure adequate packaging line clearance. However, we cannot evaluate the adequacy of your response because you failed to provide this SOP. Your response also states that you evaluated the impact of this incident or previously packaged products. In your response, please provide further details regarding this evaluation.

5. Your firm has not established and followed written procedures prescribing a system for reprocessing batches that do not conform to standards or specifications and the steps taken to insure that the reprocessed batches will conform with all established standards, specifications, and characteristics [21 C.F.R. § 211.115(a)], nor does your firm perform reprocessing with the review and approval of the quality control unit [21 C.F.R. § 211.115(b)].

For example, during the packaging of Gemfibrozil Tablets, 600 mg, lot 90076A, on August 6, 2009, you emptied under-filled bottles into the hopper for repackaging without an approved written procedure and without the approval of the QCU.

Your response acknowledges that you conducted "non-quality related reprocessing operations" without QCU approval and that an impact assessment was performed. Your response also states that packaging operations ceased on March 25, 2010, and will not resume until appropriate corrective actions are implemented. We cannot assess the adequacy of your response because you have not provided any documentation such as your impact assessment, revised packaging procedure, and enhancements to your Quality System to ensure similar deviations are identified during the Quality Unit's review of production records.

In addition, our inspection revealed that you failed to submit NDA Field Alert Reports to FDA in compliance with 2 C.F.R. § 314.81(b)(1)(ii), as required by section 505(k) of the Act [21 U.S.C. § 355(k)]. 21 C.F.R. § 314.81(b)(1)(ii) requires an applicant to submit information within three working days of date of discovery concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of drug product to meet the specifications established for it in the application. Specifically:

a. On September 30,2009, multiple lots of Gemfibrozil Tablets, 600 mg, 500 and 1000 count were noted by your Quality Unit to have imploded in the sample room. After noting this physical deterioration, Gemfibrozi Tablets, 500 count, were distributed into interstate commerce from March 25, 2009 through September 1, 2009. No Field Alert Report was filed for this incident.

b. From September 8, 2008, to December 16, 2009, fourteen consumer complaints of leaking and sweating Nimodipine Capsules, 30 mg, were received. After assessment by your QCU, a corrective action plan was implemented which included changes to your drug product formulation and soft gelatin capsule shell. These changes took place in June 2009. A Field Alert Report was not reported until March 15, 2010, when FDA conducted an inspection of your facility.

c. From May 19, 2009, to January 13, 2010, five complaints of two lots of Oxycodone Tablets, 5 mg and 30 mg (lots 90072 and 90069A) were received. Complaints ranged from under-filled bottles to a missing bottle in a packaging shipper. Because Oxycodone is a controlled substance (Schedule II) under the Controlled Substance Act [21 U.S.C. § 801 *et seq*.], all tablets should be accounted and reconciled. An NDA/ANDA Field Alert Report was provided on March 24, 2010, when FDA conducted an inspection of your facility.

Your response is inadequate because your corrective actions to address Field Alert Reporting do not comply with the requirement of 21 C.F.R. § 314.81. Your response indicates your complaint handling procedures will be revised to prevent recurrence of the drug product quality defects; however no details of your revised procedures were provided.

The violations cited in this letter are not intended to be an all inclusive list of violations that may exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations. It is your responsibility to assure compliance with all requirements of federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of new drug applications listing your facilities, until the above violations are corrected. FDA may re-inspect to verify corrective actions have been completed.

Within fifteen (15) working days of receipt of this letter, please notify this office in writing of the specific steps you have taken to correct violations. Include an explanation of each step taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Additionally, your response should state if you no longer manufacture or distribute the drug products manufactured at these facilities, and provide the date(s) and reason(s) you ceased production.

Your response should be addressed to: U.S. Food and Drug Administration, 10 Waterview Boulevard, 3rd Floor, Parsippany, New Jersey, 07054, Attn: Sarah A. Della Fave, Compliance Officer.

Sincerely,

/s/

Diana Amador-Toro
District
Director
New Jersey District

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