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

Sun Pharmaceutical Industries Ltd. 12/17/15

Department of Health and Human Services

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

WARNING LETTER

VIA UPS

WL: 320-16-04

December 17, 2015

Mr. Avinash Joshi
Quality Head SPIL Halol
Sun Pharmaceuticals Industries Ltd.
Halol-Baroda Highway, Halol,
Gujarat, 389 350, India

Dear Mr. Joshi:

From September 8-19, 2014, investigators from the U.S. Food and Drug Administration (FDA) inspected your pharmaceutical manufacturing facility, Sun Pharmaceutical Industries Ltd., Halol-Baroda Highway, Halol, Gujarat.

We identified significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, Title 21, CFR, 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 FD&C Act), 21 U.S.C. 351(a)(2)(B). 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 October 10, 2014, response in detail. It lacks sufficient corrective actions. We acknowledge receipt of your additional correspondence of December 12, 2014; February 10, 2015; and May 5, 2015.

Our investigators observed specific violations during the inspection, including, but not limited to the following.

1. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

a. You failed to perform adequate unidirectional airflow studies (smoke studies) under dynamic conditions to determine how the movement of air and personnel during aseptic operations could pose risks to product sterility. In addition, the studies indicate that your aseptic processing equipment is not properly designed. For example, an audit of your smoke studies found:

- Significant airflow turbulence, including air moving in an **(b)(4)** direction, in the laminar airflow (LAF) unit in which aseptic **(b)(4)** and tubing connections are made for the **(b)(4)** process. Also, the studies lacked dynamic simulation of this critical intervention.

- No dynamic smoke studies to demonstrate unidirectional airflow during the manual aseptic transfer of **(b)(4)** units into the **(b)(4)** used for transport to the **(b)(4)**.
- Inadequate evaluation of airflow patterns in your stopper **(b)(4)** area, and turbulence around the stopper **(b)(4)**.
- Lack of smoke studies during aseptic filling line setup activities.
- Operators **(b)(4)** open filled vials when adjusting the stopper **(b)(4)**, which is a hazard to sterility assurance.

Without smoke study data to demonstrate unidirectional airflows over all aseptic operations and processing steps, you cannot show that your processes are designed to prevent microbiological contamination or provide adequate assurance of product sterility.

In your response to the FDA-483, you acknowledged the need for design improvements and new airflow studies. You also proposed to revise your smoke study protocol **(b)(4)** to cover all aseptic interventions and material movement, and to conduct smoke studies by November 15, 2014. Your firm has submitted neither a revised smoke test **(b)(4)**, nor a satisfactory new smoke study.

In response to this letter, perform and send a video of new dynamic smoke studies that fully evaluate unidirectional airflow during your aseptic manufacturing operations, and a copy of your revised smoke test **(b)(4)**. Also explain how your firm will be comprehensively evaluating the design of your aseptic processing operation, and describe any major equipment and facility upgrades that are planned.

b. You rejected vials during media fills without written justification or explanation.

Your media fill reconciliation records failed to include a specific description of the reason why your firm rejected vials from each batch. Although a significant number of media-filled units were rejected with no written justification, you found the media fill runs in the following table acceptable.

Table 1. Media Fill Runs & Total Rejected Vials

Batch	***Manufacturing Date (dd/mm/yy)***	***Number of Filled Units***	***Number of Filled Units Rejected***
(b)(4) Products			
(b)(4)	08/07/14	**(b)(4)**	360
(b)(4)	25/06/14	**(b)(4)**	1690
(b)(4)	24/12/13	**(b)(4)**	43
(b)(4) Products			
(b)(4)	03/08/13	**(b)(4)**	453
(b)(4)	09/07/13	**(b)(4)**	51
(b)(4)	15/03/13	**(b)(4)**	529

Your media fill batch records did not include further rationale for rejecting these vials, although your “Process Simulation Using Media Fill” SOP PAR-095/09 states that the types of rejected vials must be identified before incubation. During the inspection, your deputy general manager and your Quality Assurance (QA) manager confirmed that the rejected vials were discarded during the media fill process without assignable causes recorded or documented.

Your media fill batch record also failed to adequately document non-routine interventions performed to simulate the aseptic manufacturing operation for **(b)(4)** (injection USP) **(b)(4)** mg/mL, **(b)(4)** mL, and **(b)(4)** mL. In addition, you failed to define and justify the most challenging conditions for each media fill performed (e.g., fill volume, container size, maximum hold times, personnel present during aseptic filling, **(b)(4)** operations, routine and non-routine intervention, assuring routine use of **(b)(4)** rather than **(b)(4)**) as required in your “Process Simulation Using Media Fill” SOP PAR-095/09.

Your response is inadequate for reasons including, but not limited to, the following.

- Your response appropriately committed to remove no more units than that specified in production SOPs regarding local line clearances. However, you still allowed for removal of units in media fills based on a subjective “normal practice” judgment. Local clearances are appropriate in media fills only if production SOPs clearly specified the number of units to clear and the type of intervention.

- You failed to include adequate improvements to your media fill procedure to ensure that you account for each filled and rejected vial in future media fills more specifically and quantitatively.
- The current standard for maintenance clearances was open-ended (e.g., “at least” **(b)(4)** units are cleared). The type of maintenance clearances and associated clearance requirements should be better defined.
- Units with minor defects to a **(b)(4)** were classified as non-integral.
- You failed to explain how your reliance on non-specific information on types of interventions and reasons for vial rejections affected the conclusions of your media fill studies. You did not show how you can rely on the results of your media fills to conclude that your aseptic process operation for**(b)(4)** (injection USP) **(b)(4)** mg/mL, **(b)(4)** mL, and **(b)(4)** mL was in a state of control.
- You did not perform a comprehensive evaluation to determine whether you increased customer risk by accepting units in commercial batches that would have been removed in a media fill.
- Your revised SOP PAR-095/09 and your revised media fill batch records did not specify limits and adequate descriptions for rejects, nor did they indicate what you do if the number of rejects exceeded your acceptance limit.

In response to this letter, include a risk assessment regarding your practice of rejecting media fill vials without a written justification and acceptance limits. Also provide your revised SOP on media fills, specifically addressing the changes you have made related to rejection and investigation of non-integral vials. Include specific data from all media fills conducted following your revised SOP to demonstrate its effectiveness.

For our current thinking on this topic and others relating to aseptic processing of sterile drugs, see our guidance for industry, *Sterile Drug Products Produced by Aseptic Processing-Current Good manufacturing Practice,* at http://www.fda.gov /downloads/Drugs/.../Guidances/ucm070342.pdf.

2. Your firm failed to maintain floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable in aseptic processing areas (21 C.F.R. 211.42(c)(10)(iv) and (i).

The floors, walls, and ceilings in your aseptic processing area were not maintained as smooth, hard surfaces that were easily cleaned. Our investigator documented the presence of leaks in the form of water stains and ceiling damage in the parenteral manufacturing area personnel corridor. The FDA investigator observed buckets with water collected from ceiling leaks and other leaks in this manufacturing area.

During the inspection, we noted that your Engineering Department investigated the leaks. However, you failed to address environmental control in the parenteral manufacturing area during the period of concern, or to determine how leaks in this area could compromise the quality of your aseptically-filled products.

In your response of October 10, 2014, you committed to conduct an overall assessment regarding the potential for rain water leakage by October 30, 2014, and to revise the Engineering “Procedure for Building Maintenance” SOP ENG-033. You also proposed revising QA “Reporting & Compliance of **(b)(4)** Observations” SOP QA-078 to include **(b)(4)** QA monitoring of the facilities. We acknowledge receipt of these revised procedures. However, your response is inadequate because it did not include a retrospective assessment of your environmental control (including but not limited to environmental monitoring data) in the affected areas.

In response to this letter, provide a summary of your environmental data and other facility maintenance since the inspection. Address the impact on environmental control from the start of the leakage and for the subsequent six months. Include all instances in which fungi or bacterial sporeformers were identified, and also explain to what extent microbial identifications were done in these areas. Provide all microbial results from the affected area and its immediately adjacent rooms, and describe any adverse trends or results at or above action levels. Explain the potential effects on quality of the drug products manufactured during this period and include a summary of your risk assessment.

3. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications whether or not the batch has already been distributed (21 CFR 211.192).

a. Your July 6, 2010, Out-of-Specification (OOS) report 141/2010 documented "other unknown impurities" in a 6-month accelerated stability test of **(b)(4)** mg/**(b)(4)** mL **(b)(4)** Injection manufactured for the European market, exhibit batches **(b)(4)**. Under **(b)(4)**, you also manufactured this drug for distribution in the U.S. market.

You attributed the failures to product degradation from your **(b)(4)** process, but you failed to identify the specific impurities or their root causes. You did not extend your investigation to batches distributed in the United States. You also failed to notify the FDA of these stability failures.

Further, the unknown peaks were not thoroughly investigated. According to your response, you conducted your investigation at your Sun Research & Development facility (the R&D facility), a separate facility in **(b)(4)**.

Your response is inadequate because it did not include a comprehensive assessment of the "informal" investigations of drug quality test data generated by your R&D facility.

Decisions to retest samples should be based on a strong scientific rationale and predetermined testing objectives. Any retesting plan should also include the maximum number of retests. These rationales and criteria should be specified in advance, in a written investigative protocol. For more information about handling OOS results, refer to FDA's *Guidance for Industry: Investigating Out-of-Specification (OOS) Test Result for Pharmaceutical Production, October 2006.*

In your October 2014 response, you also stated that you tested **(b)(4)** exhibit batches of **(b)(4)** mg/**(b)(4)** mL **(b)(4)** Injection from lots **(b)(4)** for the U.S. market as your impurity investigation progressed. According to your summary, all test results were within specification.

The fact the impurity levels were within specification for these exhibit batches does not justify the failure to conduct a thorough investigation into the significance of the peaks and to identify all affected batches, including those intended for the U.S. market. Your investigation did not identify a root cause or source of the impurities. You provided no justification to support your assertion that the impurities are from the **(b)(4)** process, and proposed to reduce **(b)(4)** assurance by ceasing **(b)(4)** without first determining whether the impurities pose any meaningful toxicological risk.

In response to this letter, please provide a progress report on your efforts to identify the noted unknown peaks.

b. You failed to initiate an investigation for an extraneous peak identified during the analysis of **(b)(4)** residue in your cleaning validation report for **(b)(4)** tablets, **(b)(4)** mg, lot **(b)(4)** (dated August 20, 2011). Your cleaning validation report concluded that the extraneous peak was caused from contamination while handling the sample. You have not provided a scientific rationale or evidence to support this conclusion.

You did not initiate an investigation to determine the root cause for this extraneous peak at the time of the event. You stated that you began an "informal" investigation at the time of the event and later incorporated the informal findings in a formal investigation. However, you did not provide evidence of the informal testing you conducted, nor did you indicate whether the results were included as part of your later documented investigation. You did not document a deviation regarding "informal" testing of the solutions.

In response to this letter, provide your formal investigation, including quantitative results obtained and copies of all raw data (e.g., laboratory notebooks; other records) from both the informal and formal investigations.

4. Your firm failed to establish and document the accuracy, sensitivity, specificity and reproducibility of test methods employed by the firm (21 C.F.R. 211.165(e)).

Analytical method validation demonstrates that a testing procedure is suitable for its intended use. The outcomes of method validation are important to assess the quality, reliability and consistency of analytical results.

a. You did not evaluate the accuracy of your dissolution test method for **(b)(4)** tablets, **(b)(4)** mg by UV during method validation in your January 10, 2009 analytical method validation report #MJ/ANAR/597 "Determination of Dissolution of **(b)(4)** in **(b)(4)** tablets, **(b)(4)** mg by UV Method."

In your response, you stated that you based your method validation on a May 12, 2007 method validation master plan that did not require accuracy studies. However, both the Sun Corporate "Validation of analytical methods used for the evaluation of drug products" SOP CALS-034/03 (March 3, 2011) and your site "Validation of analytical methods used for the evaluation of drug products" SOP QCS-074/01 (May 30, 2013) require accuracy studies. We acknowledge your response that you completed the supplemental validation for **(b)(4)** tablets, **(b)(4)** mg and your plan to review the completeness of validation (e.g., UV methods) for other products made at your site. We will evaluate the analytical raw data and associated chromatograms, and your more comprehensive remediation, during our follow-up inspection.

b. Your November 21, 2007 method validation failed to evaluate the capacity to separate unknown late-eluting peaks for **(b)(4)** mg/**(b)(4)** mL, **(b)(4)** Injection, high performance liquid chromatography (HPLC) Related Substance Method II, (STP #0011409) MJ/ANAR/467.

In your October 2014 response, you stated that your revised method, including a **(b)(4)** chromatographic run time to detect unknown late eluting peaks, was approved by FDA on February 25, 2014.

Your response is inadequate in that you asserted that the analytical method was properly validated. Our investigators documented repeated revisions to this method that suggested that your method was not promptly and adequately improved after first detecting and investigating the impurities in 2010 and continuing after the revised method was approved. Recent events include the following.

- Between January 2013 and September 2014, you repeated the analysis of 42 samples because of improper peak shape and merged peaks.
- On March 22, 2014, you again revised the method to ensure proper separation between late eluting peaks and adjacent blank peaks.
- In your response of October 10, 2014, you referenced late-eluting peak resolution issues found in a lot of **(b)(4)** finished product.
- In your response of October 10, 2014, you reported that you revised your method again on September 19, 2014, to address resolution of the late eluting peaks.

These repeated revisions to your analytical method STP #0011409 indicate that **(b)(4)** method may not have been properly validated and was not promptly improved. In your response to this letter, discuss how your firm's quality system oversees test method adequacy and assures needed improvements.

c. During a walkthrough of your microbiology laboratory on September 8, 2014, the investigator observed that sterile gloves intended for use in the manufacture of sterile products were partially immersed in **(b)(4)** medium. The investigator found that the fingers of the gloves were not immersed; the "Testing Procedure for Sterile **(b)(4)** Gloves" SOP lacked a requirement for full immersion of gloves in sterility test media; and the test method was not validated.

In your response to this letter, provide your revised test procedure and validation report.

5. Your firm failed to routinely calibrate, inspect, or check according to a written program designed to assure proper performance and to maintain adequate written records of calibration checks and inspections of automatic, mechanical, or electronic equipment, including computers, used in the manufacture, processing, packing, and holding of a drug product (21 C.F.R 211.68(a)).

Since 2005, you have been using an un-validated and unqualified Agilent data acquisition unit (DAU) to monitor the temperature of the microbiological incubation rooms for media filled vials. During our inspection, your quality engineer officer and QA manager stated that the DAU has not been qualified, and that you have not used a preventative maintenance schedule for this equipment during the nine years that it has been in use.

Your October 10, 2014 response confirmed that you have no records documenting qualification of the DAU. Because this equipment was never qualified or validated, it is unclear whether it accurately monitored the temperature in your incubation rooms. You indicated that you would requalify the DAU. We acknowledge the corrective actions and will verify them upon re-inspection.

6. Your firm failed to establish appropriate controls over computers and related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel (21 CFR 211. 68(b)).

You lacked audit trails or other sufficient controls to facilitate traceability of the individuals who access each of the programmable logic controller (PLC) levels or Man-Machine Interface (MMI) equipment. You had no way to verify that individuals have not changed, adjusted, or modified equipment operation parameters.

Access to production equipment used in parenteral manufacturing and solid **(b)(4)** dosage forms used a password shared by four or five individuals to gain access to each individual piece of equipment and access level. During our inspection, your Executive Production and QA manager confirmed that the password was shared. Neither your operators nor your supervisors had individual passwords.

During our inspection, firm officials also confirmed that you had not established or documented a control program to describe the roles and responsibilities of production equipment system administrators. There was also no record documenting the individuals who have access to the production equipment or the manner in which individual personnel access production equipment.

In your response, you indicated that you have performed a comprehensive review of the PLCs and manufacturing equipment associated with the production of parenteral and solid **(b)(4)** dosage forms to assess your access controls and traceability to individual operators. You suggested that traceability to the individual operator could be determined through a hybrid system using the batch manufacturing record and equipment logbook. However, because you used shared login credentials that did not permit identification of a specific person using the shared login, you have not shown how your hybrid system could link specific actions to a specific operator.

In your response, you also stated that you will conduct a retrospective risk assessment to evaluate the effects of your deficient computerized system controls on the quality of the products manufactured using this automated equipment. However, you did not indicated the timeframe for your review, your criteria for evaluating the effects of these deficiencies on your products, or any actions needed for products within expiry.

Finally, in your response, you indicated that you planned to **(b)(4)**. Your response is inadequate because you did not indicate what controls you will implement in the interim to assure that only authorized personnel change your production or other records.

In response to the letter, provide your retrospective review and risk assessment of lots manufactured using equipment with shared passwords. Explain how you will identify which operators or personnel performed and recorded specific activities, your criteria for evaluating how manufacturing and quality of your products has been affected by your deficient controls, and any actions needed to assure the quality, safety, and efficacy of products within expiry.

Conclusion
These examples are serious CGMP violations. Your quality system does not ensure the quality, safety, and effectiveness of your drug products. It is essential that executive management systematically improve their oversight of manufacturing quality to ensure sustainable quality assurance.

We acknowledge your commitment to work with a third party consultant to conduct a comprehensive assessment of your firm's manufacturing, laboratory, and quality operations. However, it is your responsibility to ensure that the third party audit includes a full evaluation of your systems, operations, procedures, and documentation practices, and that you implement appropriate changes in response.

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for determining causes, for preventing recurrence, and for preventing other violations.

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of active pharmaceutical ingredients and/or finished products produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Staff 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 Staff also allows you to meet any obligations you may have to report discontinuances in your drug manufacture 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 take corrective action without interrupting supply, or to shorten any interruption, thereby avoiding or limiting drug shortages.

Until you complete all corrections and we have confirmed your compliance with CGMP, we may withhold approval of any new applications or supplements listing your firm. We may also refuse admission of articles manufactured at Sun Pharmaceutical Industries Ltd., Halol-Baroda Highway Halol, Gujarat, into the United States under Section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3).

Articles may be subject to refusal of admission pursuant to Section 801(a)(3) of the FD&C 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 FD&C Act, 21 U.S.C. 351(a)(2)(B).

Within 15 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 violation. If you cannot complete corrective actions within 15 working days, state the reasons for the delay and the date by which you will have completed the corrections. Send your reply to:

Cesar E. Matto
Compliance Officer
U.S. Food and Drug Administration
White Oak, Building 51, Room 4235
10903 New Hampshire Ave
Silver Spring, MD 20993

Please identify your response with FEI #3002809586.

Sincerely,
/S/
Thomas Cosgrove, J.D.
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

More in 2015 (/ICECI/EnforcementActions/WarningLetters/2015/default.htm)