Cadila Pharmaceuticals Limited 2/25/15

Department of Health and Human Services

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

Warning Letter

WL: 320-15-02

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

AMENDED
(This letter replaces Warning Letter No. 320-15-02 dated October 15, 2014)

February 25, 2015

Dr. Rajiv A. Modi
Chairman & Managing Director
Cadila Pharmaceuticals Limited
Cadila Corporate Campus
Sarkhej, Dholka Road, Bhat
Ahmedabad 382 210 Gujarat
India

Dear Dr. Modi:

During our March 24-28, 2014 inspection of your pharmaceutical manufacturing facility, Cadila Pharmaceuticals Limited located at 294 GIDC Industrial Estate, Ankleshwar, Gujarat, India, an investigator from the U.S. Food and Drug Administration (FDA) identified significant deviations from current good manufacturing practice (CGMP) for the manufacture of active pharmaceutical ingredients (APIs). These deviations cause your 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 response dated April 10, 2014 and note that it lacks sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondence dated May 2, 2014 and June 30, 2014.

Our investigator observed specific deviations during the inspection, including, but not limited to, the following:

1. Failure to adequately investigate complaints and extend the investigations to other batches that may have been affected.

Since 2011, your firm has failed to fully investigate and implement corrective actions related to complaints. For example,

a. In September 2011, your firm received a customer complaint for an unpleasant odor for batch **(b)(4)** of **(b)(4)** API. The investigation into this complaint concluded that the control of **(b)(4)**, a known impurity, may be related to the odor detected, and the investigation was closed in October 2011, before the implementation of the proposed corrective actions. In addition, your investigation did not provide data to support your conclusion. There is no assurance that the changes to the manufacturing process, implemented in response to the odor complaints, were correlated to the odor issue.

In response to this letter, provide a chronology of the changes made to the **(b)(4)** API manufacturing process to control the process impurities since September 2011. Include documentation of any changes that may have affected the impurity profile of **(b)(4)** API since September 2011.

b. In August 2012, your firm received another customer complaint for an unpleasant odor for batches **(b)(4)** and **(b)(4)** of **(b)(4)** API. In addition, the complainant reported the failure of **(b)(4)** API batch **(b)(4)** for maximum unknown impurity (at **(b)(4)**%, exceeding the specification of not more than **(b)(4)**%).

The investigation concluded that the unpleasant odor was related to the presence of **(b)(4)**, a process impurity. The data to support your March 19, 2014 investigation conclusion regarding **(b)(4)** levels in your **(b)(4)** API batches was not retained. As part of the investigation, your firm reintegrated multiple chromatograms to determine **(b)(4)** levels; however, the parameters for the reintegration were not retained.

During the inspection we were provided with reintegration results for batch **(b)(4)** that showed an **(b)(4)** level of **(b)(4)** ppm; however, the reintegration results provided in your written response to the Agency related to this same batch indicated that **(b)(4)** was “not detected.” In response to this letter, explain the discrepancy found between the data provided during the inspection and the data provided in your response.

Your firm’s response states that your established specification for **(b)(4)** is not more than **(b)(4)** ppm. Provide the details of your scientific justification to support the use of **(b)(4)** ppm as a specification.

Also, describe the controls implemented to prevent recurrence of **(b)(4)** levels exceeding your in-house specification and explain your assurance that commercial batches of **(b)(4)** API within expiry meet your in-house specification.

Your investigation related to the out-of-specification (OOS) result for the maximum unknown impurity for batch **(b)(4)**, concluded that the impurity had carried over from a raw material used in the API manufacturing process. This investigation did not address the failure of the quality unit to recognize this impurity OOS prior to release.

Include in your response information regarding the controls you have in place to prevent the use of raw material containing the undesirable impurity that was responsible for the **(b)(4)** API batch **(b)(4)** failure. In addition, provide a chronology for the implementation of your revised raw material controls and a detailed assessment of batches still within expiry that were manufactured prior to the implementation of these controls.

2. Failure of your quality unit to exercise its responsibility to ensure the APIs manufactured are in compliance with CGMP, and meet established specifications for quality and purity.

a. Your firm released **(b)(4)** API batch **(b)(4)** with an unknown peak present in the residual solvents chromatogram. Although this unknown peak was not a part of your historical impurity data, neither the analyst nor the supervisor apparently noticed or evaluated this unknown peak during their reviews.

Subsequently, a customer complaint was received for this batch, and your investigation identified the unknown peak as **(b)(4)**. Your firm found that this peak was a result of a contamination that occurred during your manufacturing process.

Your firm's response failed to provide adequate assurance that appropriate controls have been implemented to mitigate recurrence of contamination during manufacturing operations. Provide an assessment of the cross-contamination risks due to your current practices for the material flow of solvents, and any corrective actions resulting from this assessment. Also, provide an assessment of the contamination risk for batches within expiry.

In response to this letter, provide the corrective actions implemented to ensure that all laboratory data is appropriately analyzed, accurately reported and approved by your quality unit.

3. Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data.

Your firm did not have proper controls in place to prevent the unauthorized manipulation of your electronic raw data. For example,

a. The inspection found that the audit trail feature for your gas chromatography (GC) instruments was not used until October 2013, even though your 2009 GC software validation included a satisfactory evaluation of the audit trail capability.

b. There is no assurance that you maintain complete electronic raw data for the **(b)(4)** GC instruments, the Malvern particle size analyzer, and the ultraviolet (UV) spectrophotometer. Our inspection found that these instruments were connected to stand-alone computers that stored the data and that the data could be deleted.

c. Prior to our inspection, your firm failed to have a back-up system for the data generated by one of the **(b)(4)** Fourier transform infrared spectrometers, the polarimeter, the UV spectrophotometer and the Malvern particle size analyzer.

Your response states that data from these, as well as other laboratory instruments is now saved on a central server and that a new LIMS system will be installed in October 2014. Your response provided an interim solution for electronic raw data retention. Provide any additional steps that you are taking to assure integrity of your electronic raw data.

In response to this letter, provide a copy of your plan(s) to validate the processes of archiving and restoring your electronic data.

We also note that numerous stability samples have not been tested at the required intervals. Specifically, the inspection found that your 2014 stability program was in backlog and that samples were overdue for testing. In addition, we are concerned that your quality unit was not aware of this backlog situation.

In response to this letter, provide information that compares the 2014 delayed results to the expected API impurity profile at the originally planned test intervals. Also, provide the planned schedule for resolution of the backlog.

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

The items listed above, as well as other deficiencies our investigator found, lead us to question the effectiveness of your current quality system to achieve overall compliance with CGMP at your facility. It is apparent that you have not implemented a robust quality system at your firm. Be advised that corporate management is responsible for ensuring the quality, safety, and integrity of products manufactured by Cadila Pharmaceuticals Limited. FDA strongly recommends that your corporate management immediately undertake a comprehensive evaluation of global manufacturing operations to ensure compliance with CGMP expectations.

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 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.

Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm’s compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as an API manufacturer. In addition, your failure to correct these violations may result in FDA refusing admission of articles manufactured at Cadila Pharmaceuticals Limited in Ankleshwar, 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 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. Also, if you no longer manufacture or distribute the APIs at issue, provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3002806711.

Please send your reply to:

Regina T. Brown, Senior Policy Advisor
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance, Office of Manufacturing and Product Quality
Division of International Drug Quality
White Oak, Bldg. 51, Room 4248
10903 New Hampshire Ave.
Silver Spring, MD 20993.

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