Inspections, Compliance, Enforcement, and Criminal Investigations

Wockhardt Limited 11/25/13

Department of Health and Human Services

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

Warning Letter

WL: 320-14-01

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

November 25, 2013

Dr. Habil Khorakiwala
Founder, Chairman & Group CEO
Wockhardt Limited
Bandra Kurla Complex, Bandra (East)
Mumbai, Maharashtra 400 051, India

Dear Dr. Khorakiwala:

During our July 22-31, 2013 simultaneous inspections of your pharmaceutical manufacturing facilities, Wockhardt Limited (FEI 3002808503) located at L-1, M.I.D.C. Area, Chikalthana, Aurangabad, Maharashtra, India, and Wockhardt Limited (FEI 3004540156) located at B-15/2, M.I.D.C. Area, Waluj, Aurangabad, Maharashtra, India, investigators from the U.S. 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 have conducted a detailed review of your firm’s responses and note that they lack sufficient corrective actions.

We also acknowledge receipt of your firm's additional correspondence dated October 2, 2013. Our investigators observed specific violations during the inspection, including, but not limited to, the following:

1. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

For example, our investigators identified your practice of performing “trial” sample analysis for high performance liquid chromatography (HPLC) analyses at your Chikalthana and Waluj facilities prior to acquiring the “official” analytical data for release and stability testing.

Chikalthana Facility (FEI 3002808503):

The FDA investigators observed your practice of performing "trial" injections for HPLC analyses used to test content uniformity, assay, and dissolution for release and stability for at least **(b)(4)** different products.

The investigator observed that for finished product **(b)(4)** Tablets **(b)(4)** mg, batches **(b)(4)**, your firm performed "trial" injections. The inspection documented that an HPLC run had an injection sequence named as **(b)(4)** assay, **(b)(4)** assay **(b)(4)**, and **(b)(4)** assay **(b)(4)** attributed to the "trial" injections. Our investigators noticed that the injection sequence names used the **(b)(4)** digits of the previously referenced batch numbers. During the inspection, your firm's management was unable to determine whether the "trial" injections were performed using standard solutions or actual batch samples. Based on the HPLC data, these "trial" injections occurred on 5/7/13. Later that same day, it appears that the "official" sample analyses were performed for batches **(b)(4)**. The assigned names for the sequence injections creates the perception that your QC operator named the vials using the **(b)(4)** digits of the batch numbers to link the "trial" injections for the batches with the official assay analyses. We are concerned because our investigator noticed that the "trial" injection data related to batch **(b)(4)** rendered an out-of-specification (OOS) result for the **(b)(4)** and **(b)(4)** assays. Therefore, it appears that the batch **(b)(4)** did not pass the "trial" analysis but met specifications when the "official" sample was tested shortly thereafter.

In addition, our investigator discovered that some of the "trial" injection data was not kept on the HPLC hard drives because your firm deleted it. Your firm's management confirmed that the files were deleted as part of an internal audit conducted as a result of the March 2013 FDA inspection at your nearby Wockhardt Limited facility located in Waluj (FEI: 3005289335).

Waluj Facility (FEI 3004540156):

Our investigators found similar instances of the use of "trial" injections stored in default folders on the HPLC hard drive for at least four drug products. The inspections documented that both sites have SOPs that allow the use of "trial" injections. For example, the Waluj site's procedure, SOP QA/GLP/08 "*HPLC Analysis"* mentions that standard and sample injections are allowed to ensure system equilibration before the system suitability runs are performed. Neither the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) document Q2R, "Validation of Analytical Procedure: Text and Methodology," nor the United States Pharmacopoeia General Chapter <1058> , "Analytical Instrument Qualification," includes instructions for performing "trial" injections for a method that is validated.

The lack of reliability and accuracy of data generated by your firm's laboratory is a serious CGMP deficiency that raises concerns about the integrity of all data generated by your firm. We are also concerned that your quality unit allowed the practices of "trial" injections (about **(b)(4)** "trial" injections) and deletion of HPLC files to persist without implementation of sufficient controls to prevent data manipulation.

Moreover, your firm's second response to the FDA 483 dated October 2, 2013 essentially confirms that actual samples were used as "trial" injections. It appears that QC analysts attempted to mask the practice of performing sample "trial" injections by labeling them as standards rather than by the actual batch numbers or other identifying information.

We are particularly concerned about your inability to implement a robust and sustainable quality system. The findings from our current inspections include repeat citations from FDA's inspection of the Wockhardt Waluj, Aurangabad, India facility conducted in March 2013. These repeated observations and citations indicate that your quality unit is not exercising its responsibilities and may not have the appropriate authority or ability to carry out its responsibilities.

The Agency is concerned about Wockhardt's responses to these matters. Among other things, although Wockhardt was made aware of a major product defect/problem during FDA's March

22, 2013 inspection at a Wockhardt facility located in Biotech Park, MIDC area Waluj, Aurangabad, India, you did not take appropriate actions to resolve the "trial" sample injection problem discussed above at the Biotech Park facility or elsewhere within Wockhardt's organization. Senior management is responsible for ensuring the quality, safety, and integrity of your firm's products. Implementing adequate controls to prevent the manipulation of laboratory data, assuring timely investigation and resolution of product defects, and preventing distribution of defective products are all fundamental aspects of these responsibilities.

In response to this letter, provide a comprehensive plan describing how you will implement appropriate corrective actions globally.

2. 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)).

Chikalthana Facility (FEI 3002808503):

The inspection documented that all of your QC laboratory computerized instruments (**(b)(4)** HPLCs) were found to be stand-alone, and laboratory personnel demonstrated that they can delete electronic raw data files from the local hard drive. Your firm deleted multiple HPLC data files acquired in 2013 allegedly to clear up hard drive space without creating back-ups. Your QC management confirmed that there is no audit trail or other traceability in the operating system to document the deletion activity. Furthermore, your analysts do not have unique user names and passwords for the computer and laboratory information systems; your QC analysts use a single shared user identifier and password to access and manipulate multiple stand-alone systems.

Waluj Facility (FEI 3004540156):

The **(b)(4)** HPLC systems in operation at the Waluj facility are also stand-alone, and during our inspection, an employee demonstrated to the investigator that data can be deleted through the local hard drive of the data acquisition system. As with the Chikalthana facility, all Waluj facility employees use a shared password to access the operating system. During the inspection, your firm's management informed our investigator that **(b)(4)** back-ups of data are performed. However, we are concerned that your system and procedures permit deletion of HPLC files and that **(b)(4)** backed up data may not represent all the original data generated.

You are responsible not only for having controls to prevent alteration or loss of the data, but also for recording any changes made to existing data, which should include the date of change, identity of the person who made the change, and an explanation or reason for the change.

In response to this letter, provide your evaluation of all laboratory equipment that may be affected by the lack of adequate controls to prevent data manipulation. In addition, address the root cause of your quality unit's failure to control and detect the manipulation or alteration of laboratory documents and describe actions to prevent recurrence. In response to this letter, provide your procedures to manage all computerized data and how the data will be used, retained and stored to ensure its integrity.

3. Your firm failed to follow written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess, and to document same at the time of performance (21 CFR 211.100(b)).

At your Chikalthana site, our investigators observed poor documentation practices during in-process testing. Specifically, an operator performed the in-process tablet **(b)(4)** testing for the **(b)(4)** mg tablet batch #**(b)(4)** without the batch record or a manufacturing form to document the results contemporaneously. The FDA investigator was informed that the pre-test and post-test weight values are documented in the batch record located in a separate manufacturing room rather than in the same room where the actual weights are measured. Moreover, your operator stated that he records the two weights with **(b)(4)**

significant figures into the batch record from memory. Your investigation into this issue is inadequate because it did not consider other in-process tests or whether the operator(s) have been involved in the same poor documentation practices for others batches. Your response does not indicate whether this poor documentation practice is an isolated case or is a matter of widespread behavior in this facility.

Additionally, the investigator noticed that the balance used in production was not level, which can result in inaccurate weights. The investigator asked how long the balance had not been level, and you indicated that you would investigate the matter and respond to the investigator. To date, you have not responded to FDA explaining your resolution of this matter.

In response to this letter, provide your firm's assessment as to whether any other batches have been impacted by the poor documentation practices. Also provide the status of all production balance calibrations, your calibration procedure, and explain whether any other balances or other equipment have been similarly compromised and your evaluation of this problem.

4. Your firm failed to follow a written testing program designed to assess the stability characteristics of drug products (21 CFR 211.166(a)).

Chikalthana Facility (FEI 3002808503):

Our investigators observed two open bottles of **(b)(4)** mg capsules batch #**(b)(4)** with **(b)(4)** missing capsules. According to the stability study protocol, **(b)(4)** bottles were placed in the chamber and **(b)(4)** had been tested. Therefore, **(b)(4)** sealed bottles should still be in the chamber. Also for **(b)(4)** mg capsules batch #**(b)(4)**, the opened bottle had **(b)(4)** capsules missing. Your quality control unit did not know why those bottles were opened or why capsules were missing.

Your response indicates that, in order to determine the cause for the missing capsules, you performed a complete review of the stability analytical data for the **(b)(4)** mg capsules batch concluding that no repeat analyses were performed and the missing capsules were probably the result of analyst error. However, as described in citation # 2 of this letter, FDA has found that your firm's CGMP deviations include the deletion of HPLC raw data files without the creation of back-ups. As such, we have no assurance that your firm can support your conclusion that no repeat analyses were performed.

Waluj Facility (FEI 3004540156):

The inspection documented that for **(b)(4)** batch **(b)(4)**, the three and six-month time points were both tested on April 22, 2012. Also, you placed batch **(b)(4)** in the stability chamber on May 2, 2012. Accordingly, the three-month test interval should have been August, 2012. However, you did not conduct your three-month interval tests for this batch until a full six months had elapsed, on October 5, 2012. The same issue of late testing was observed at the six-month time point.

We are concerned both because your quality unit was unable to detect these deficiencies, and because you failed to initiate an investigation into these deficiencies until our investigators brought them to your attention during our inspection. Our review of the significance of current findings indicates that your quality unit is not fully able to exercise its responsibilities. It is essential that you provide the quality unit with the appropriate authority, staff, and resources to carry out its responsibilities.

Your response indicates that you will procure stability scheduler software to track and monitor your stability plans and their execution as per written stability programs.

In response to this letter, provide your action plan to ensure that these improvements to your stability program will be followed throughout all of your facilities. Also explain how the stability scheduler software will ensure the stability sample accountability is carried out as is established in the approved stability protocol.

Finally, we note again that the CGMP violations listed in this letter include similar violations to those cited in the WL 320-13-21, issued on July 18, 2013. It is apparent that Wockhardt is not implementing global and sustainable corrective actions. It is essential that your firm implement a robust quality system. We remind you that you are responsible for ensuring that your firm's drug manufacturing operations comply with applicable requirements and produce acceptable quality drugs. FDA strongly recommends that Wockhardt's executive management immediately undertake a comprehensive and global assessment of your manufacturing operations to ensure that your systems and processes, and ultimately, the drug products you manufacture, conform to FDA requirements for safety, efficacy, and quality.

The violations cited in this letter are not intended to be an all-inclusive list of violations that 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.

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could 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.

As requested above, provide your corrective action plan that describes your commitment, procedures, actions, and controls to ensure data integrity. This plan should include the corrective actions implemented to ensure that all managers, supervisors, and quality unit personnel are properly trained in detecting data integrity and manipulation issues. The investigation should provide detailed descriptions of other incidents where your quality unit failed to ensure proper testing of materials and should include a retrospective review of all test results generated by your laboratory personnel. If other instances of missing, inaccurate or unreliable test results are found, your investigation should assess the impact of these discrepancies on the quality of the drug products manufactured at your facility. Provide the documentation of specific training offered to all employees regarding the importance of following CGMP and ensuring that all required tests are performed.

We highly recommend that you hire a third party auditor, with experience in detecting data integrity problems, to assist you with this evaluation and to assist with your overall compliance with CGMP. It is your responsibility to ensure that data generated during operations is accurate and that the results reported are a true representation of the quality of your drug products. In response to this letter, provide a list of all the batches of drug products shipped to the U.S. market that relied upon missing, inaccurate, or unreliable test data.

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 period(s) 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 data 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 identified in item (5) above are still in a position to influence data integrity with respect to CGMP requirements or the submission of applications; and establish procedures to expand your internal review to any other facilities determined to be involved in or affected by the inaccurate data reporting.

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 a drug product manufacturer. In addition, your failure to correct these violations may result in FDA refusing admission of articles manufactured at Wockhardt Limited (FEI 3002808503) located at L-1, M.I.D.C. area, Chikalthana, Aurangabad, Maharashtra, India and Wockhardt Limited (FEI 3004540156) located in B-15/2, M.I.D.C. area, Waluj, Aurangabad Maharashtra, 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 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 product(s) at issue, provide the date(s) and reason(s) you ceased production. Please identify your responses with FEI # **3002808503** and **3004540156**.

Please send your reply to:

Rafael Arroyo
Compliance Officer
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Manufacturing and Product Quality
Division of International Drug Quality
White Oak, Building 51 room 4235
10903 New Hampshire Ave.
Silver Spring, MD 20993

Sincerely,
/S/
Steven J. Lynn
Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

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Silver Spring, MD 20993
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