Inspections, Compliance, Enforcement, and Criminal Investigations

Wockhardt Limited 7/18/13

Department of Health and Human Services

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

Warning Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL: 320-13-21

July 18, 2013

Dr. Habil Khorakiwala
Chairman & Group CEO
Wockhardt Limited
Biotech Park, Plot H-14/2
M.I.D.C. Area: Waluj
Aurangabad, India

Dear Dr. Khorakiwala:

During our March 18, 2013 through March 22, 2013 inspection of your pharmaceutical manufacturing facility, Wockhardt Limited located at Biotech Park, Plot H-14/2, M.I.D.C. Area Waluj, Aurangabad, 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, and documented that your firm withheld truthful information, and delayed and limited the inspection. These violations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) and 501(j) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 351(a)(2)(B) and 351(j), 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, and in that your drug products have been manufactured, processed, packed, or held in an establishment and the owner or operator has delayed, denied, or limited an inspection, or has refused to permit entry or inspection, respectively.

We have conducted a detailed review of your firm's response of April 9, 2013 and note that it lacks sufficient corrective actions.

1. Your firm repeatedly delayed, denied, limited an inspection or refused to permit the FDA inspection. Examples are as follows:

   a. On March 18, 2013, an FDA investigator identified the presence of torn raw data records in the waste area and asked one of your firm's QA Officers to remove these torn raw data records for the investigator's review. This QA Officer presented the FDA investigator with approximately 20 paper records, none of which included raw data entries identified in the waste area earlier during the inspection. The FDA investigator asked three times if there were any more records found in the waste area, and the QA Officer

responded to each question, "no, this is all of the records". The FDA investigator then re-visited the waste area and found that the raw data records had been removed and placed in a different holding bag. These records included raw data testing worksheets from anti-microbial effectiveness studies, controlled Master Batch Records for **(b)(4)** (**(b)(4)**)", equipment calibration records, and stability protocol records. Because you provided some, but not all, of the records requested by the investigator that FDA had the authority to inspect, you limited access to or copying of records for the FDA inspection. Because you directed FDA investigators away from the requested documents, and because the FDA investigator was impeded by having to locate and reassemble torn records that FDA had requested and had the authority to inspect, you delayed the inspection.

b. On March 18, 2013, an FDA investigator identified the presence of unlabeled and partially labeled vials in the laboratory glassware washing area. When the investigator asked a QC Analyst to describe the contents of these vials, the QC Analyst immediately began dumping the contents of the vials into the drainage sink. The QC Analyst stated that the content of the vials could not be determined. Because you limited the direct observation by the FDA investigator and prevented any determination of the contents of the unlabeled vials, you limited the inspection.

c. On March 19, 2013, an FDA investigator interviewed the Production Head regarding his knowledge of the unofficial batch record forms being used to record the results for the visual inspection of drug products. The Production Head stated that he had only seen this unofficial defect data for "1 to 2 batches". The FDA investigator had an earlier conversation with two manufacturing operators, who stated that the Production Head had directed this practice throughout the manufacturing facility and regularly requested and reviewed the unofficial BMR visual inspection results. On March 21, 2013, the Production Head stated that he was fully aware of the practice of using unofficial batch record copies during the course of manufacturing operations. The Production Head acknowledged that he had provided inaccurate information in the previous instances. By stating that the data that existed was limited to one or two batches and that no other data existed, you provided some, but not all, of the records requested by the investigator that FDA had the authority to inspect. Additionally, you limited access to or copying of records for the FDA inspection. Because you denied the existence of records that FDA had requested and had the authority to inspect in order to obstruct the direct observation of the requested documents, you delayed the inspection.

d. On March 18, 2013, your Vice President of Manufacturing stated on three different occasions that the facility inspected **(b)(4)** aseptic filling line for all products (vials and pre-filled syringes) produced for the U.S. market. However, the FDA investigators later identified **(b)(4)** aseptic filling line for pre-filled syringes manufactured for export to the U.S. market, in use since at least September 2009. The area was operational and was an area of the inspection site that FDA has authority to inspect. The FDA investigator was impeded at the inspection site from properly performing the inspection in a reasonable manner. Because you directed the FDA investigator away from this production area, you obstructed the direct observation of the manufacturing process to an unreasonably short amount of time, and you limited the inspection. Because the investigator only later discovered the existence of the area, you delayed the inspection.

e. On March 20, 2013, an FDA investigator requested the QC data package and raw data testing documentation for **(b)(4)** tablets Batch #**(b)(4)**, **(b)(4)** and **(b)(4)** batch # **(b)(4)**, and **(b)(4)** tablets batch #**(b)(4)**. The investigator repeated the request no less than six times on March 20, 2013, and again multiple times on March 21, 2013. The data was provided to the FDA investigator during the close-out meeting of the inspection on March 22, 2013. You failed to produce the requested records within the timeframe requested by the investigator without adequate justification. By delaying the provision of requested data and documents until the last scheduled day of the inspection without reasonable explanation, you limited the ability of the investigator to review and analyze the documents to an unreasonably short amount of time and you delayed the inspection.

Our investigators observed specific CGMP violations during the inspection, including, but not

limited to, the following:

2. Your firm failed to prepare batch production and control records for each batch of drug product that include documentation of the accomplishment of each significant step in the manufacture, processing, packing, or holding of the batch (21 CFR 211.188(b)).

For example, on March 18, 2013, the FDA investigators found unofficial batch records for approximately 75 batches of injectable finished drug products torn in half in a waste area. These records contain data indicating that some batches failed to meet the in-process visual inspection specifications of not more than **(b)(4)**% defects, while the official batch records for these batches state that these batches had met the specifications. The uncontrolled documents indicate that up to 14% of vials had defects including, but not limited to, black particles, fibers, glass particles, sealing defects, and volume variations. According to your firm's procedures, a defect rate higher than **(b)(4)**% requires initiation of an investigation; however, a senior production officer at your firm stated that no investigations are performed when this occurs.

Your firm's response indicates that these issues are for products not related to the U.S. market, and that they pertain solely to the Formulation **(b)(4)** building. Additionally, you indicate that the Quality Unit is not involved in the use of uncontrolled records. You also indicate that your firm re-inspected the batches referenced in the FDA observation. You provided an affidavit from your senior production officer stating "Each and every identified defect unit during in-process visual inspection was rejected and only good units were transferred to the next stage for 100% visual inspection after filling."

Your response is inadequate because your facility manufactures **(b)(4)** Injection in pre-filled syringes for the U.S. market in the same Formulation **(b)(4)** building where these torn records were observed. Your response did not address why your quality unit is not performing its duty to control records used in the manufacture of your drug products. Your investigation for the products listed in the Form FDA 483 was limited and failed to include all of the other drugs manufactured by your facility. Your affidavit confirms that your firm uses unofficial visual inspection to remove the defective units from the production line without appropriate documentation and investigation.

The above examples raise serious concerns regarding the integrity, reliability and accuracy of the data generated and available at your facility. In your response to this letter, provide an independent and comprehensive evaluation of the extent of the deletion and destruction of records, a risk assessment regarding the potential impact on the quality of products, and a comprehensive corrective and preventive action plan. Your submission should include a summary report of your evaluation of the data and records related to the manufacture (including testing, holding, etc.) of all drug products produced at your site. This evaluation should include a detailed investigation of other instances in which your operations and quality units failed to ensure proper testing of materials, review of laboratory results and production data. For all other instances of missing, inaccurate or unreliable tests results are found, describe these findings in your response to this letter. Your investigation should assess the impact of all these incidents on the quality of the drug products manufactured and released into distribution, and explain the systemic actions that will be instituted to prevent these fundamental breaches of data integrity and management oversight in the future.

Accordingly, you should include a detailed description of your plans to implement a robust quality system in your response to this letter. This remediation plan should describe the broader steps you will be taking to ensure direct corporate oversight over the quality and operations functions of this facility. This system should ensure sustainable compliance with CGMP, including the basic capability to prevent data manipulation and destruction of records.

3. 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, your firm's laboratory records failed to include complete records of all stability testing performed. The FDA investigators identified the practice of performing "trial" sample analysis for High Performance Liquid Chromatography (HPLC) analyses prior to collecting the "official" analytical data for stability testing. These "trials" were performed on multiple products,

including **(b)(4)** Tablets **(b)(4)**mg, **(b)(4)**mg/**(b)(4)**ml, and **(b)(4)** Tablets. These trial runs were not recorded in the equipment use log, and sample preparation data associated with these analyses was destroyed, preventing any calculation or analysis of the resulting data. Your response states that trial runs were conducted using only one of the **(b)(4)** HPLC instruments located in the stability laboratory, which happened to be the one instrument that the FDA investigators reviewed during the inspection. Your response indicates that you have revised procedures and re-trained your staff.

Additionally, your quality control HPLC raw data files can be deleted from the hard drive using the common PC login used by all **(b)(4)** analysts. This deletion eliminates all records of sample injections and analyses. Your response indicates that this deletion function is only available on the software used for one of **(b)(4)** sets of HPLC instruments. You also indicated that you have changed the access control privileges such that laboratory analysts in a "user" role cannot delete or rename files.

We also note that on March 20, 2013, your Quality Control Analyst stated to the investigator that he had used "other samples" to complete the test methods for **(b)(4)** Injection, USP (**(b)(4)**mg/ml).

Your response is inadequate because you failed to provide the root cause for the unacceptable practice of performing undocumented "trial" runs at your facility, failed to expand the scope of your investigations to include other instruments that use computerized electronic records both inside and outside the stability laboratory, and failed to provide risk assessments on all the drugs where samples had been tested by these instruments. Your response failed to completely address how your firm will ensure the integrity and completeness of all analytical raw data.

In response to this letter, address your evaluation of all laboratory equipment and any other process-related 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.

4. Your firm failed to record and justify any deviations from required laboratory control mechanisms (21 CFR 211.160(a)).

The FDA investigators identified a memo dated March 12, 2013 (a week before the inspection), documenting a computer "crash" that occurred on the central back-up and controller PC for **(b)(4)** HPLC instruments. The memo describes the loss of instrument activity logs (audit trails). Our investigators found that several of the HPLCs had the audit trail functions disabled; therefore, there is no assurance that the data generated using these HPLCs is accurate. Your response indicates that your firm performed an assessment of the historical HPLC chromatograms (raw data) generated on each individual HPLC unit prior to March 12, 2013 and verified it against previously printed chromatograms. Based on this analysis, your firm claimed that you had confirmed that the backup data is available for each of the analyses and no analytical data has been lost due to the computer crash. However, your firm failed to provide a risk assessment for the products tested using the HPLC instruments that had the audit trail functions disabled. This is especially noteworthy given the fact that prior to the inspection, at least one QC officer had the ability to delete data on the affected system.

The lack of reliability and accuracy of data generated by your firm's laboratory is a serious CGMP deficiency that raises concerns with all data generated by your firm. While we acknowledge the commitment in your response to improve quality assurance, we remain concerned that your investigation was not comprehensive enough to determine the extent and impact of the problem. We are particularly concerned about your inability to implement a robust and sustainable Quality System. These findings include repeat citations from the January 2012 inspection and indicate that your quality control unit is not exercising its responsibilities and may not have the appropriate authority or ability to carry out its responsibilities.

5. 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, on March 18, 2013, FDA investigators identified the presence of incomplete

training "Questionnaire" records. Per your training procedures, these questionnaire forms must be completed following each training to assess the individual's competence. The inspection documented over 40 instances of incomplete training records for three of your staff members. In each case, the trainee and trainer names were left blank on the questionnaires, but were pre-filled with the answers. Incomplete training records were found for critical GMP activities, including:

- Handling of sterilized materials and materials to be sterilized
- Handling and transfer of media fill vials
- Line clearance for the manufacturing, filling, washing and sealing areas, sanitized container storage area and sanitization area
- Replacement of filters and integrity testing frequency
- Operation of filter integrity tester
- Qualification of personnel for aseptic area

Your response indicates that these are not GMP documents and that the FDA investigators' concerns were limited to the department-specific training. Your response did not include a review of all other training documents to determine whether assessments had been appropriately completed and assessed.

In your response to this letter, provide your plan to develop a robust CGMP training program for your personnel, and how you intend to assess the effectiveness of the training.

6. Your firm failed to provide adequate washing and toilet facilities to working areas (21 CFR 211.52).

For example, our investigators found that the washing and toilet facility located approximately twenty (20) feet (approximately 6 meters) from the entrance/gowning area to the Sterile Formulation **(b)(4)** manufacturing facility was found to have urinals that lacked drainage piping. The urine was found to fall directly onto the floor, where it was collected in an open drain. Stagnant urine was observed near the open drain. In addition, the investigators also observed what appeared to be mildew or other mold(s) in this toilet facility. The facilities used in the manufacture of drugs should be appropriately maintained and repaired, and remain in a clean condition.

In your response, you acknowledged your failure to have adequate washing and toilet facilities. Your response is inadequate because you failed to provide documented evidence that your updated cleaning procedures and studies demonstrate effectiveness. We are concerned that your firm has been cited for inadequate cleaning and sanitary conditions during previous inspections, and that your responses to these citations promised corrective actions; however, our inspections continue to reveal problems in this area of CGMP.

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. 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 non-existent, 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.

In summary, you are responsible for having controls to prevent omissions of data, as well as, recording any changes made to existing data, which should include the date of change, identity of person who made the change, and an explanation or reason for the change. All changes to existing data should be made in accordance with an established procedure.

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. Provide a list of all the lots of drug products shipped to the U.S. market that relied upon missing, inaccurate, or unreliable test data.

The CGMP expert should:

1. Perform a comprehensive inspection of the facilities, method, and controls used to manufacture drugs, and determine whether your facilities, method, and controls used to manufacture drugs are in compliance with CGMP requirements.
2. Evaluate whether your facilities have established and implemented a comprehensive written QA/QC program that is adequate to ensure continuous compliance with CGMPs requirements.
3. Evaluate whether your facilities have established and implemented an adequate stability program that accurately measures the stability characteristics of drug products.
4. Evaluate whether your firm has established and implemented a comprehensive written program to maintain production, control, and other records and to ensure the authenticity and reliability of all data reflected in those records.
5. Evaluate adequacy of data integrity training for all staff who perform CGMP activities. Identify gaps and implement ongoing training modules on the responsibility of all staff to assure authentic records. This training should also instruct your firm’s managers in detection of data integrity and manipulation practices. At minimum, staff from development, quality, operations, and regulatory affairs should be trained.

The data integrity consultant should:

1. Identify any historical period(s) during which inaccurate data occurred at your facilities.
2. Identify and interview your current employees who were employed prior to, during, or immediately after the relevant period 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 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) of this subparagraph are

still in a position to influence data integrity with respect to CGMP requirements or the submission of applications; and establishing procedures to expand the internal review to any other facilities determine 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 continuing to refuse admission of articles manufactured at Wockhardt Limited located at Biotech Park, Plot H-14/2, M.I.D.C. Area Waluj, Aurangabad, 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 response with FEI # 3005289335.

Please send your reply to:

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Sincerely,
/Michael D. Smedley/
Michael D. Smedley
Acting Director
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