檔　　號：
保存年限：

衛生福利部食品藥物管理署　函

地址：11561 臺北市南港區昆陽街161-2號
聯絡人：蘇子婷
聯絡電話：0227877148
傳真：0227877178
電子信箱：daisyhaha@fda.gov.tw

受文者：中華民國西藥代理商業同業公會

發文日期：中華民國106年1月10日
發文字號：FDA風字第1061100096號
速別：普通件
密等及解密條件或保密期限：
附件：原料藥廠違反GMP警訊乙份(A21020000I106110009601-1.pdf)

主旨：美國FDA發布印度原料藥廠「Wockhardt, Ltd. 」（廠址：Plot No. 138 G.I.D.C. Estate District Bharuch, Ankleshwar, Gujarat, India）Warning Letter乙案，詳如說明段，請轉知所屬會員知照。

說明：

一、美國衛生主管機關US Food and Drug Administration（FDA）查核旨揭原料藥廠，判定嚴重違反CGMP，並於105年12月23日正式發布Warning Letter（詳如附件）。

二、鑑於旨揭原料藥之製造品質無法符合GMP之要求，可能對藥品製造品質帶來影響與危害，請轉知所屬會員釐清相關輸台製劑產品是否使用旨揭原料藥廠所生產原料藥，並應依風險管理原則辦理相關後續處置。

正本：中華民國西藥商業同業公會全國聯合會、中華民國西藥代理商業同業公會、台北市西藥代理商業同業公會、中華民國開發性製藥研究協會、中華民國藥品行銷暨管理協會
副本：2017-01-11 交09:42:19章

Wockhardt, Ltd. 12/23/16

U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Ave.
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-17-13

December 23, 2016

Dr. Habil Khorakiwala
Founder, Chairman and Group CEO
Wockhardt Limited
Bandra Kurla Complex, Bandra (East)
Mumbai, Maharashtra 400051
India

Dear Dr. Khorakiwala:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Wockhardt Limited, Plot No. 138 G.I.D.C. Estate District Bharuch, Ankleshwar, Gujarat, from December 7 to 15, 2015.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, 21 CFR parts 210 and 211, and significant deviations from CGMP for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drugs are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your January 15, 2016, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigator observed specific violations and deviations including, but not limited to, the following.

Sterile API Violations

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)).

During the airflow analysis (smoke study) of aseptic connections on your **(b)(4)** equipment inside the laminar air flow (LAF) ISO-5 area, our investigator identified air flow disturbances and turbulence. Under dynamic conditions, air did not sufficiently sweep across and away from sterile connections, so the sterility of any product processed under these conditions could be compromised.

Furthermore, in our review of the smoke study, we identified multiple aseptic technique breaches during aseptic connection of the **(b)(4)** equipment. Your equipment design and aseptic processing operator competencies appear to contribute to the lack of unidirectionality. Aseptic processing equipment should provide for appropriate ergonomics that enable operators to reproducibly conduct aseptic manipulations. In addition, it is critical that your aseptic processing operators have the knowledge and skills to practice strict aseptic techniques. Even operations that have been successfully qualified can be compromised by poor operational, maintenance, or personnel practices.

In response to this letter, perform a full review of aseptic processing equipment design and aseptic techniques. Provide your corrective and preventive action (CAPA) plan. Include a video DVD of all smoke studies for LAF-711, LAF-712, and LAF-713 conducted following CAPA implementation.

2. Your firm failed to ensure that manufacturing personnel wear clothing appropriate to protect drug product from contamination (21 CFR 211.28(a)).

Our investigator observed employees working in gowns that had unraveled stitching extending from hoods, zippers, and pants. Your firm approved these gowns for operations. Employees wore them while manufacturing sterile **(b)(4)** USP API and sterile **(b)(4)** API. Five of 10 garments released for use in aseptic production areas had loose fibers or other damage. Per your procedures, you should have discarded these garments. You determined that inadequate lighting and ineffective operator training were root causes.

Your response is inadequate because it does not include your assessment of washing, drying, ironing, sterilizing, or other operations that may contribute to sterile garment damage. It also does not address the need to limit the number of sterilizations. Our investigator noted that you sterilize gowns numerous times. These excessive sterilizations lead to breakdown of gown fibers.

Your aseptic processing gowns were inadequate to prevent contamination of your sterile products with particles and microorganisms shed from employees' bodies. Your firm must use garments that are suitable for aseptic processing.

In response to this letter, provide an action plan that describes how your firm will do the following.

- Select appropriate gown suppliers. Include the role of the quality unit in making supplier selection and ongoing qualification decisions.
- Reduce your maximum number of gown sterilizations to ensure that gowns are discarded before they show signs of breakdown. Provide the maximum number of re-sterilizations you will allow, and describe how you will document and validate this procedure.
- Correct your visual inspection procedures for sterile garments to improve detection and rejection of defective garments.
- Ensure that the quality unit makes final decisions relating to release of raw materials and supplies (e.g., garments) you use in production.
- Conduct a risk assessment of the effects of damaged garments on your drugs.

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)).

While reviewing gas chromatography data on instrument QA/G07, our investigator found unreported results, including an out-of-specification (OOS) test result for raw materials. You did not investigate this OOS result or explain why you excluded the failing result from the official record.

Our investigator also found that you reported only two of three chromatographic injections of sterile **(b)(4)** batch **(b)(4)** during in-process **(b)(4)** sample testing for residual solvent. You did not explain why you excluded the third injection. You decommissioned this instrument in July 2014 without reviewing the instrument data.

Your response indicates that you have initiated a retrospective review of high performance liquid chromatography (HPLC) and gas chromatography (GC) data over a multi-year period. Your response is inadequate because it does not explain the depth of your electronic data review, or commit to a comprehensive retrospective review of raw data from all laboratory equipment and systems.

In response to this letter, include a detailed update of the HPLC and GC electronic chromatographic data review. Include the total number of injections during the period, the number that your retrospective audit examined, and all anomalies and deviations observed. Specify the date of the test, products involved, all relevant results obtained, and batch (or other purpose) for which the testing was done. See Data Integrity Remediation caption below for our full request, including a determination of whether the data may have been associated with any drug applications.

4. 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)).

Our investigator found that you have not validated 12 computerized systems in your quality control laboratory. These systems are used for your stability chambers, ultraviolet (UV) and infrared (IR) spectrophotometers, and for thin layer chromatography (TLC).

We acknowledge your commitment to validate your computerized systems. However, your response is inadequate.

In response to this letter, include your assessment of the data generated from these stability chambers, UV and IR spectrophotometers, and TLC equipment.

API Deviations

5. Failure to record activities at the time they are performed, and destruction of original records.

Data Recorded in Personal Diaries (Unofficial Notebooks)
In your process development laboratory, our investigator found several unofficial notebooks recording sample preparation for OOS investigations, route-of-synthesis experiments, and scale-up data. Our investigator found discrepancies between these unofficial notebooks and the official data retained by your quality unit.

Destruction of CGMP Documentation
CGMP documentation was discarded without being assessed by your quality unit. Our investigator found torn and shredded equipment maintenance documents, raw material labels, and change control work orders in your scrap yard awaiting incineration. Your staff lacked knowledge of your corporate procedure for the destruction and incineration of documents.

In your response, you indicate that you have implemented corporate procedure CQA/021 to address the destruction of uncontrolled and controlled documents, and that you have retrained your employees.

Your response is inadequate because you did not assess how your document-control practices affected your distributed products.

Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation.

In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:

- A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
- An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
- A comprehensive retrospective evaluation of the nature of the testing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential batches were identified should evaluate all data integrity lapses.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analysesof the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include:

- A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA.
- A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.
- Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
- Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
- A status report for any of the above activities already underway or completed.

Conclusion

Violations and deviations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations and deviations, for determining the causes, for preventing their recurrence, and for preventing other violations and deviations in all your facilities.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA 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 or interruptions in your drug manufacture under 21 U.S.C. 356C(b) 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.

FDA placed your firm on Import Alert 66-40 on August 5, 2016.

Until you correct all violations and deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations and deviations may also result in FDA continuing to refuse admission of articles manufactured at Wockhardt Limited, Plot No. 138 G.I.D.C. Estate District Bharuch, Ankleshwar, Gujarat, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles may be subject to refusal of admission, 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).

After you receive this letter, respond to this office within 15 working days. Specify what you have done since our inspection to correct your violations and deviations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to **CDER-OC-OMQ-Communications@fda.hhs.gov (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov)** or mail your reply to:

Rafael Arroyo
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3002808500.

Sincerely,
/S/
Francis Godwin
Acting Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

More in 2016 (/ICECI/EnforcementActions/WarningLetters/2016/default.htm)