檔　　號：
保存年限：

衛生福利部食品藥物管理署　函

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受文者：中華民國西藥代理商業同業公會

裝

發文日期：中華民國106年2月13日
發文字號：FDA風字第1061100885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(A21020000I106110088500-1.pdf)

主旨：美國FDA發布印度原料藥廠「CTX Lifesciences Private Ltd. 」（廠址：Block No: 251/P, 252/P, GIDC, Sachin-Magdalla Road Surat, Gujarat 394230 India）Warning Letter乙案，詳如說明段，請轉知所屬會員知照。

訂

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106年1月18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。

線

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：2017-02-14 08:58:58 收文章

CTX Lifesciences Private Ltd. 1/18/17

U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-17-18

January 18, 2017

Mr. Kanak J. Jariwala
Director
CTX Life Sciences Pvt., Ltd.
Block No: 251/P, 252/P, GIDC, Sachin-Magdalla Road
Surat, Gujarat 394230
India

Dear Mr. Jariwala:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, CTX Life Sciences Private Ltd. (CTX), at Block No: 251/P, 252/P, GIDC, Sachin-Magdalla Road, Surat, Gujarat, from February 15–19, 2016.

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API 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 March 9, 2016 response in detail and acknowledge receipt of your subsequent correspondences.

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

1. Failure to have adequate cleaning procedures to prevent contamination or carry-over material that would alter API quality.

Our investigator observed rust, insects, damaged interiors, and/or drug residues in **(b)(4)** of **(b)(4)** pieces of manufacturing equipment. This equipment was identified as "clean" and was either in direct contact with API or could potentially contact API. Your deficient cleaning and maintenance practices present an unacceptable risk of introducing foreign contaminants, or cross-contamination between drugs.

According to your response, you have initiated a corrective action and preventive action (CAPA) to de-stain and repair manufacturing equipment. However, your response is inadequate as it does not detail improvements made to cleaning procedures, your overall maintenance program, or your investigations into batches manufactured utilizing this equipment.

In response to this letter:

- Summarize how you ensure that equipment is appropriately indicated as clean before starting a new batch. Detail how you improved existing processes and procedures to ensure that equipment is adequately cleaned prior to use.
- Provide cleaning validation studies to demonstrate that your cleaning procedures are adequate for worst case API cross contamination scenarios. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity, and stability.
- A CAPA plan to globally upgrade your maintenance program, including more extensive preventive maintenance improvements.
- Include your risk assessment of batches released for distribution to the U.S. that were potentially compromised by inadequate equipment cleaning and maintenance.

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

Our investigator found that on June 30, 2014, batches **(b)(4)** and **(b)(4)** of **(b)(4)** United States Pharmacopeia (USP) API were released without testing by ultraviolet (UV) spectrometry for identity or **(b)(4)** content, because the UV was out of order.

Your change control form stated, "Batches shall be released on conditional basis and as soon as UV maintenance issue rectified analysis shall be performed for identification and **(b)(4)** content."

Your June 30, 2014 certificate of analysis states "UV & **(b)(4)** result shall be updated." However, our inspection found that identity and **(b)(4)** testing was never performed. It is unacceptable to distribute batches without conducting the required quality control tests to assure your API meets its quality attributes.

In your response, you state that your UV spectrophotometer broke down. Your quality department felt the quality of the released batches was adequate because other required release tests were passed, high performance liquid chromatography (HPLC) testing was done, and trend data for **(b)(4)** was satisfactory. Your response is inadequate.

In response to this letter, provide:

- A detailed summary of all batches released without all required testing. Identify the tests you did not perform, and how you plan to ensure that released products meet specifications.
- A list of the improvements you have made to your batch release process to ensure that you do not release future batches before all required tests are completed.
- Improvements made to your existing system to ensure required equipment is available to conduct testing for batch release.

- A summary of your method validation study to support the use of HPLC in lieu of the compendial method for determining identity.

3. Failure to ensure all production deviations are reported and evaluated, and that critical deviations are investigated and conclusions are recorded.

Our investigator's review of your 2014 and 2015 annual product quality reviews (APQR) revealed that your firm had eight critical process parameter failures related to time limits for **(b)(4)** or **(b)(4)** operations under **(b)(4)** conditions for **(b)(4)** USP API.

For example, batch **(b)(4)**, Deviation Report D/PR/052/14 under Operation **(b)(4)** specifies that **(b)(4)** should be attained within **(b)(4)**. However, the actual **(b)(4)** time was more than **(b)(4)**. Furthermore, you failed to conduct adequate investigations into these significant deviations prior to making batch disposition decisions.

In your *Critical process parameters in manufacturing process of* **(b)(4)** document, signed on February 19, 2016, you stated, "Under **(b)(4)** condition, **(b)(4)** degrades to give the **(b)(4)** material and **(b)(4)**. The **(b)(4)** material and **(b)(4)** will react with **(b)(4)** to generate the **(b)(4)** impurity." Failure to meet time limits for **(b)(4)** or **(b)(4)** operations could lead to inconsistent strength and purity.

Your response is inadequate. Although you attribute these failures to mechanical breakdowns and operator delays, your response lacks a comprehensive assessment of how these critical deviations affected your API quality.

In response to this letter, provide:

- Test results of all batches that may have been compromised by **(b)(4)** impurities
- Evaluation of product impact when critical parameters exceeded established limits
- Data to support the root cause analysis in your March 9, 2016 response
- List of improvements in your quality system to ensure that
    - all deviations are reported to the quality unit before batch release
    - all investigations are properly performed
    - the quality unit conducts robust APQR and effective internal audits

4. Failure to ensure that test procedures are scientifically sound and appropriate to ensure that your API conform to established standards of quality and/or purity.

During a review of your customer complaints, our investigator found a September 13, 2014, complaint concerning a batch of **(b)(4)** (**(b)(4)**) that failed water content. The specification range of **(b)(4)** water content was **(b)(4)**% to **(b)(4)**%. Although your firm measured **(b)(4)**% water content during the release of the batch, the complainant measured **(b)(4)**% water content.

Your retrospective analysis concluded that your firm's laboratory reported lower water content results than your customer's laboratory obtained for all **(b)(4)** batches of **(b)(4)** you supplied to the customer. Significantly, our inspection revealed that you had not validated your method for measuring water content.

According to your response, you have completed method validation for water content. However, your response is inadequate because it does not detail your investigation into the released API batches tested using non-validated method.

In response to this letter, provide:

- Retrospective review or retesting of all batches of **(b)(4)** that remain within retest period or expiry

- A review of all test methods to ensure they are validated

Conclusion

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

Until you correct all 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 deviations may also result in FDA refusing admission of articles manufactured at CTX Life Sciences Private Ltd., at Block No: 251/P, 252/P, GIDC, Sachin- Magdalla Road, Surat, India 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, you have 15 working days to respond to this office in writing. Specify what you have done since our inspection to correct your 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:

Loan Chin
Pharmacist
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 3006254924.

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

More in 2017 (/ICECI/EnforcementActions/WarningLetters/2017/default.htm)