檔　　號：
保存年限：

正本

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

發文日期：中華民國106年5月5日
發文字號：FDA風字第1061102717號
速別：
密等及解密條件或保密期限：
附件：美國FDA Warning Letter 320-17-33 影本1分

主旨：美國FDA發布中國原料藥廠「Teva Pharmaceutical and Chemical (Hangzhou) Co. Ltd.」（廠址：No.1889 Jingliu Road, Linjiang Industrial Zone, Xiaoshan, Hangzhou, Zhejiang, China 311228）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，判定違反CGMP，並於106年4月5日正式發布Warning Letter（詳如附件）。

二、鑑於旨揭原料藥之製造品質恐無法符合GMP之要求，可能導致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：中華民國西藥代理商業同業公會、中華民國西藥商業同業公會全國聯合會、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：

署長吳秀梅

Teva Pharmaceutical and Chemical (Hangzhou) Co. Ltd. 4/5/17

U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS

Warning Letter 320-17-33

April 5, 2017

Mr. Quanmin Ye
General Manager
Teva Pharmaceutical and Chemical (Hangzhou) Co. Ltd.
No.1889, Jingliu Road, Linjiang Industrial Zone,
Xiaoshan, Hangzhou, Zhejiang, China 311228

Dear Mr. Ye:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Teva Pharmaceutical and Chemical (Hangzhou) Co. Ltd., 1889 Jingliu Road, Xiaoshan, Hangzhou, Zhejiang, China from September 26 to 29, 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 October 21, 2016 response in detail and acknowledge receipt of your subsequent correspondence.

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

1. Failure to establish written procedures to monitor the progress and control the performance of processing steps that may cause variability in the quality characteristics of your API.

Our inspection found that approximately 10 percent of **(b)(4)** API batches produced at your facility from December 2014 to September 2016 failed to meet the **(b)(4)** impurity limit. During this period, an additional 10 percent of batches yielded out-of-trend (OOT) results for **(b)(4)**. You have reprocessed rejected out-of-specification OOS batches but failed to implement effective corrective and preventive actions (CAPA) to correct process design and control flaws that lead to excessive formation of this impurity during processing.

According to your response, a new root cause analysis found that impurity failures appear to be related to insufficient control of **(b)(4)**. You committed to monitor **(b)(4)** specific process parameters in the new process performance qualification batches of **(b)(4)** API and the first **(b)(4)** commercial batches. However, these proposed parameters differ from the "critical process parameters" monitored by your firm in the last three years. They also do not include all of the parameters that you categorized as "critical and significant" in the most recent process qualification study. Your response does not commit to monitor future batches for all parameters that impact quality, and may contribute to the failure of a batch of intermediates or API to meet specifications.

Your response is also inadequate because it did not include the risk assessment and related scientific rationale to ensure that controls implemented for all batches will detect upstream processing variation and ensure final API quality. You also acknowledged in March 2017 correspondence that additional lots have failed since you resumed commercial manufacture of **(b)(4)** API. Recurrence of product quality failures following the completion of your investigation and process re-qualification indicate that your root cause analysis and CAPA were ineffective.

In response to this letter:

- Provide an updated investigation into the root cause(s) of **(b)(4)** OOS results and an improved CAPA plan. Include provisions to ensure CAPA effectiveness.
- Specify if the presumed root causes for failures were actually observed in the failed **(b)(4)** batches.
- Describe why some finished **(b)(4)** API batches yielded OOS results for the **(b)(4)** impurity, but passed testing for this same impurity at the **(b)(4)** stage.
- List the past and current process parameters for **(b)(4)** API. Explain their role in the process, the potential impact on quality, the limits used, and your justification if you plan to cease monitoring and controlling any parameter during commercial batch manufacture.
- Explain your systems for incorporating reprocessing activities into Drug Master Files.
- Provide procedures that ensure that reprocessed lots and process performance qualification lots are included in your stability program.

2. Failure to establish a sampling plan based on scientifically-sound sampling practices.

Our investigator documented deficiencies in your validation sampling plan for **(b)(4)** API. You did not conduct adequate monitoring and testing during process performance qualification stage to evaluate whether product quality was uniform throughout each batch. You only assessed water content at the drying step for homogeneity.

In your response, you acknowledged that a higher level of sampling during the revalidation of the manufacturing process revealed some inter-batch variability in residual solvents and particle size distribution of **(b)(4)**.

Your response is inadequate because it did not describe how your continued process verification program assures that quality attributes continue to be met batch-to-batch, as well as uniformly throughout each batch. Regarding uniformity, using only **(b)(4)** samples for attributes that may significantly vary within a batch is insufficient to ensure that your process remains in an ongoing state of control.

In response to this letter:

- Specify how you will improve batch sampling of **(b)(4)** API to ensure that you detect intra- and inter-batch variability during commercial manufacturing.

- Evaluate other API produced by your firm for adequacy of sampling plans.
- Provide overall quality system improvements to ensure all sampling performed by your firm is representative and able to detect non-uniformity of the quality attributes that may vary within a batch.

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.

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 Teva Pharmaceutical and Chemical (Hangzhou) Co. Ltd., 1889 Jingliu Road, Xiaoshan, Hangzhou, Zhejiang 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 in writing within 15 working days. 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:

Rebecca Parrilla
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 3009271645.

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)