檔　　號：
保存年限：

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發文日期：中華民國105年7月1日
發文字號：FDA風字第1051103439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(A21020000I105110343900-1.pdf)

主旨：美國FDA發布德國原料藥廠「BBT Biotech GMBH」（廠址：Arnold-Sommerfeld-Ring 28, Baesweiler, Germany）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5月16日正式發布Warning Letter（詳如附件）。

二、鑒於旨揭原料藥廠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
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U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

BBT Biotech Gmbh 5/16/16

Department of Health and Human Services

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

Warning Letter 320-16-12

Via UPS
Return Receipt Requested

May 16, 2016

Mr. Hans Peter Oeltze
Head of Quality Assurance
BBT Biotech Gmbh
Arnold-Sommerfeld-Ring 28
Baesweiler, Germany 52499

Dear Mr. Oeltze:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, BBT Biotech GMBH at Arnold-Sommerfeld-Ring 28, Baesweiler, Germany, from May 4–7, 2015.

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 May 26, 2015, response in detail and acknowledge receipt of your subsequent responses.

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

1. Failure to follow a documented, on-going stability testing program to monitor the stability characteristics of API and to use the results to confirm appropriate storage conditions and retest or expiry dates.

You did not follow your stability program, SOP No. Q-0007. According to your SOP, you must fully test at least **(b)(4)** batch of **(b)(4)** API **(b)(4)** for stability at defined stability intervals. Your firm could not provide any stability data to support the **(b)(4)** expiration date assigned to your **(b)(4)** API.

For example, since January 2012, you shipped approximately **(b)(4)** batches of **(b)(4)** API to the United States for which you have no stability data to support your expiration dates. Without stability data for your API, you could not assure that your API met specifications when used by your customers.

We acknowledge your commitment to follow your SOP and perform the required stability testing on future batches. However, your response was inadequate because you failed to include any retesting of the API already distributed.

In response to this letter, provide data evaluating whether all API batches potentially in United States supply chain within expiry are stable for the assigned **(b)(4)** expiration date.

2. Failure to establish and follow a change management system evaluating all changes that could affect the production and control of your API, and failure to evaluate the potential effect changes may have on the quality of your API.

Your firm did not have a change management program. You did not require the quality unit to review or approve changes in suppliers. In 2012, your firm changed your crude **(b)(4)** supplier from **(b)(4)** to **(b)(4)**. In 2013, you added **(b)(4)** to your list of suppliers. You did not provide change management documentation or any other documentation for these supplier changes. Without adequate evaluation for critical raw material changes, you could not assure the acceptability of your API manufactured using materials from different suppliers.

Your response was inadequate because you failed to provide any information regarding the effect of supplier changes on the distributed API, such as the effect of changes on the impurity profile or the stability of your API.

In response to this letter, provide the following:

- a plan to establish and follow a change management program
- an evaluation of the changes on the impurity profile and stability for your API
- a risk assessment regarding the effects of your supplier changes on the distributed API

3. Failure to adequately investigate out-of-specification (OOS) results.

During the inspection, our investigators documented that lot **#(b)(4)** was rejected after it failed in-process control testing for the **(b)(4)**, which is deemed a critical in-process control (including the control point and method) for your API. Although your investigation identified the supplier change as a possible root cause for the failure, you did not evaluate other lots made with crude **(b)(4)** from the same supplier. For example, you used the same crude **(b)(4)** from the new supplier in API lot **#(b)(4)**, which you failed to evaluate before shipping to the United States.

We acknowledge your commitment to follow an updated SOP requiring a root cause analysis for in-process OOS results. However, your response was inadequate because it did not assess the effects of the failure to adequately investigate in-process OOS results or indicate how this failure may have affected your API quality.

In response to this letter, provide a comprehensive assessment of all in-process OOS results for **(b)(4)**, including root causes. Extend this assessment to other batches that might have been affected. Also provide a detailed evaluation of all in process attributes and parameters in terms of their roles in the process and impact on the product and in-process material.

4. Failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data, and to provide adequate controls to prevent omission of data.

Our investigator found that your **(b)(4)** system used for **(b)(4)** and **(b)(4)** testing lacked access controls and audit trail capabilities. For example, all employees had administrator privileges and shared one user name, so actions could not be attributed or traced to specific individuals. This exposed your electronic data to manipulation and/or deletion without traceability.

Our investigator also noted that your firm copied raw data to a CD **(b)(4)**, and then deleted the data from the **(b)(4)** system to free space on the hard drive. Files copied to the CD were selected manually; the selection process was not supervised. Without audit trail capabilities or supervised file selection, there was no assurance that all raw data files were copied to the CD before they were permanently deleted from the system.

We acknowledge your commitment to hire a third-party expert to install audit trails and other controls to ensure that data cannot be deleted from this electronic system. However, your response was inadequate. Simply preventing data deletion is not sufficient. You did not show how these steps will ensure that your firm retains and evaluates all data, including laboratory data, created as part of a CGMP record prior to release of your API.

In your response to this letter, investigate your retention and review of CGMP data and provide the results. Focus on your firm's review and retention of laboratory raw data. In addition, provide your interim plan for reviewing and retaining data while your firm is in the process of implementing access controls and audit trail capabilities.

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, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of drugs produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Staff immediately 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 Staff 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.

After you receive this letter, you have 15 business 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 business days, state your completion date and reasons for delay.

Until you completely correct all deviations and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as an API manufacturer. Failure to correct these deviations may also result in FDA refusing admission of articles manufactured at BBT Biotech Gmbh, Arnold-Sommerfeld-Ring 28, Baesweiler, 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).

Send your reply to:

Lixin (Leo) Xu, M.D., Ph.D.
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Rm. 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov

Please identify your response with FEI # 3005761912.

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)