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

發文日期：中華民國105年12月14日
發文字號：FDA風字第1051107123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(A21020000I105110712301-1.pdf)

主旨：美國FDA發布中國原料藥廠「Dongying Tiandong Pharmaceutical Co Ltd 」（廠址：No.1236, Nan-er Road, Dongying, Shandong, China）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11月10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：2016-12-14 13:56:01

Dongying Tiandong Pharmaceutical Co Ltd 11/10/16

Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-17-06

November 10, 2016

Mr. Lin Guo
General Manager
Dongying Tiandong Pharmaceutical Co., Ltd.
No. 1236 Nan-er Road
Dongying, Shandong
China 257067

Dear Mr. Guo:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Dongying Tiandong Pharmaceutical Co., Ltd. at No.1236, Nan-er Road, Dongying, Shandong, from October 12 to 16, 2015.

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

Because the methods used in, or the facilities or controls used for, manufacturing, processing, packing, or holding of your API do not conform to, or are not operated or administered in conformity with 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 November 6, 2015, response in detail and acknowledge receipt of your subsequent correspondence.

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

1. Failure to adequately investigate and document out-of-specification results according to a procedure, and implement appropriate corrective actions.

Our investigator found that your firm repeatedly, and without justification, resampled and retested crude heparin batches when your quantitative polymerase chain reaction (Q-PCR) test for ruminant DNA exceeded your established specification limit of ≤ **(b)(4)** parts per million (ppm). As a result, your firm used crude heparin batches that potentially were out-of-specification (OOS) to manufacture heparin sodium API for the U.S. market.

For example, according to your Deviation Handling Sheet No.07-2015021, you resampled and tested crude heparin batch Y102-1504005 multiple times, with the following results.

Ruminant DNA Q-PCR test results for batch Y102-1504005

	Specification (ppm)	*Value (ppm)*	*Result*
Sample one	**(b)(4)**	47.4	OOS
Sample two	**(b)(4)**	343.0	OOS
Sample three	**(b)(4)**	2.3	batch released

You neither evaluated the initial sample OOS, nor conducted retesting of the initial original sample to confirm it. Instead, you resampled until you obtained a passing result.

Similarly, your initial test results for another crude heparin batch (Y102-1503008) were also OOS. Again, you resampled without justification, and accepted the batch when you obtained results within specification.

Disregarding the OOS results, and resampling and retesting without scientific justification, constitutes "testing into compliance." This practice is unscientific and objectionable under CGMP.

Your response is inadequate because you did not adequately address how you would investigate OOS lab results prior to resampling.

For further reference regarding OOS test results, see the guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production* available online at **http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070287.pdf (http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070287.pdf)**.

In response to this letter, send us the results of your retroactive review of all Q-PCR test results for crude heparin used to manufacture API for the U.S. market. Include your detailed sampling procedure for preparing crude heparin samples for analysis.

2. 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 the inspection, our investigator reviewed your Q-PCR method to determine whether crude heparin batches you receive were contaminated with ruminant DNA. Our investigator identified deficiencies in your validation of your test method for detecting ruminant DNA, including failure to directly compare your Q-PCR method to FDA's posted method: **http://www.fda.gov/AnimalVeterinary/ScienceResearch/ToolsResources/ucm350289.htm (http://www.fda.gov/AnimalVeterinary/ScienceResearch/ToolsResources/ucm350289.htm)**

Although you performed a supplemental validation study for your ruminant DNA test method, you did not report a robust comparability study to the posted FDA method. You may use an alternate validated method; however, you must be able to demonstrate that the alternate method is as sensitive, or more sensitive, in detecting ruminant DNA as FDA's posted method. We have concerns that your test method for ruminant DNA may be inadequate.

As you have had repeated difficulty in implementing an alternate method for detecting ruminant DNA in your incoming crude heparin, we recommend that in response to this letter, you commit to implementing the FDA

method and provide a timeline for full implementation.

3. Failure to adequately monitor your crude heparin suppliers.

As part of your crude heparin supplier qualification program, you sampled material from potential suppliers and tested for ruminant DNA, among otherspecifications. If a potential supplier's material failed testing for ruminant DNA, you did not use that supplier.

However, when an already-qualified supplier provided material that failed ruminant DNA testing, you did not reject the material and reevaluate the raw material supplier's qualification status.

It is critical that your quality unit makes all supplier selection decisions, and continually evaluates the qualification status of suppliers to ensure their suitability and competence. In the event of adverse information, supplier disqualification may be necessary.

In response to this letter, please provide a list of all of your current crude heparin suppliers and your procedure to continually monitor the acceptability of your crude heparin suppliers. Also please perform a full requalification of all current crude heparin suppliers and provide a summary report of this requalification, including a list of any suppliers that have been disqualified.

4. Failure of the quality unit to ensure that all critical deviations are investigated and resolved.

During the inspection, our investigator reviewed the high pressure liquid chromatography (HPLC) assay of over-sulfated chondroitin sulfate (OSCS) for crude heparin batches Y102-1404007, Y102-1404008, Y102-1404009, Y102-1404010, Y102-1404011, and Y102-1404012. The investigator found that the heparin standard and system suitability tests were run in isolation, rather than contemporaneously, approximately10 hours after the initial assay was completed.

One of your employees explained that the analyst discovered that the system suitability sequence failed during the initial sample sequence. Instead of invalidating the associated sample results, the analyst reran the system suitability sequence with the heparin standard and the OSCS control.

Passing system suitability testing indicates that requirements for precision are satisfied and HPLC functions appropriately: in this case, detecting the contaminant OSCS in heparin. The failure of your HPLC system suitability testing calls the validity of OSCS testing performed on the same equipment into question.

We acknowledge that your SOP *Abnormal Incidents in the QC Lab*, which you provided with your response, establishes procedures for handling OOS incidents in the future.

In response to this letter, provide the results of your retrospective review of all HPLC results for OSCS. Your review should demonstrate that:

- your test results are accurate
- you document and investigate interrupted HPLC runs
- you perform passing system suitability results in the same sequence as the evaluated samples

For further reference regarding heparin, see the guidance for industry *Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality* available online at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291390.p
(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291390.

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 Dongying Tiandong Pharmaceutical Co., Ltd. at No.1236, Nan-er Road, Dongying, Shandong, 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:

Rokhsana Safaai-Jazi
Consumer Safety 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 3004395180.

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)