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1061102725號
速別：
密等及解密條件或保密期限：
附件：美國FDA Warning Letter 320-17-34 影本一份

主旨：美國FDA發布印度原料藥廠「Divi's Laboratories Ltd. (Unit II) 」（廠址：Unit-2, Chippada Village, Annavaram Post Bheemunipatnam Mandal, Visakhapatnam District, Andhra Pradesh 531162, 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，判定違反CGMP，並於106年4月13日正式發布Warning Letter（詳附件）。

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：中華民國藥品行銷暨管理協會、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

副本：

署長吳秀梅

Divi's Laboratories Ltd. (Unit II) 4/13/17

U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS

Warning Letter 320-17-34

April 13, 2017

Mr. Kiran S. Divi
Director and President of Operations
Divi's Laboratories Ltd. (Unit II)
Unit-2, Chippada Village
Annavaram Post Bheemunipatnam Mandal
Visakhapatnam District
Andhra Pradesh 531162
India

Dear Mr. Divi:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Divi's Laboratories Ltd. (Unit II) at Unit-2, Chippada Village, Visakhapatnam District, from November 29 to December 6, 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).

Additionally, our investigators documented that your firm limited and/or refused an FDA inspection. Under the FD&C Act, as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA), section 707, 21 U.S.C. 351(j), your drugs are adulterated in that they have been manufactured, processed, packed, or held in an establishment where the owner or operator has limited inspection and/or refused inspection.

We reviewed your December 24, 2016, 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 ensure that test procedures are scientifically sound and appropriate to ensure that your API conform to established standards of quality and/or purity.

Our investigators observed that the software you use to conduct high performance liquid chromatography (HPLC) analyses of API for unknown impurities is configured to permit extensive use of the "inhibit integration" function without scientific justification. For example, our investigator reviewed the integration parameters you used for HPLC identification of impurities in release testing for **(b)(4)**. These parameters demonstrated that your software was set to inhibit peak integration at four different time periods throughout the analysis. Similarly, in the impurities release testing you performed for **(b)(4)**, your HPLC parameters were set to inhibit integration at four different time periods throughout the analysis.

Inhibiting integration at various points during release testing for commercial batches is not scientifically justified. It can mask identification and quantitation of impurities in your API, which may result in releasing API that do not conform to specifications.

In your response, you stated that you have made several corrective actions, including updating your procedure *Peak Integration Techniques for Chromatography* to include controls on the use of inhibit integration events. However, your response is inadequate in that it did not provide specific corrective action or supportive documentation for each drug's chromatographic processing parameters, including API not cited on Form FDA 483. You have not shown how you will ensure that your test methods are appropriate to determine whether your API conform to established standards and specifications. Consequently, the summary data you provided does not demonstrate that previously released lots do not contain excessive levels of unknown impurities.

In response to this letter, provide updated analyses of all lots within expiry that take into account any changes to specific test methods and chromatographic parameters.

2. Failure to prevent unauthorized access or changes to data and failure to provide adequate controls to prevent manipulation and omission of data.

During the inspection, our investigators discovered a lack of basic laboratory controls to prevent changes to and deletions from your firm's electronically-stored data in laboratories where you conduct CGMP activities. Specifically, audit trail functionality for some systems you used to conduct CGMP operations was enabled only the day before the inspection, and there were no quality unit procedures in place to review and evaluate the audit trail data. For example, you used standalone HPLC (2-RD HP/SM/32) to conduct analyses for Drug Master File (DMF) submissions and investigations, such as characterization of a starting material for your **(b)(4)** DMF. You also used uncontrolled systems to conduct out-of-specification (OOS) investigations for in-process materials used to manufacture **(b)(4)** API.

We acknowledge the corrective actions described in your response, including enabling audit trail functionality for all chromatographic systems in your laboratories, as well as procedural updates that require review and evaluation of the data generated by these systems. However, your response did not demonstrate how the specific controls you have implemented prevent deletion or alteration of data, nor have you shown how you will ensure that these controls are documented, implemented, and followed.

3. Limiting access to or copying of records

Your firm limited access to or copying of records that our investigators were entitled to inspect. For example, our investigators requested records of your audit trail data from all chromatographic systems used to test drugs for the U.S. market at your facility. The files you ultimately provided (in the form of Excel spreadsheets rather than direct exports from your chromatographic software) were not the original records or true copies, and showed signs of manipulation. The records you did provide contained highlighting, used inconsistent date formats, and lacked

timestamp data; these features are inconsistent with original data directly exported from chromatographic testing software.

Our investigators and their supervisor explained at least twice that the data you provided was not representative of actual audit trail data from the chromatographic systems, and requested that you provide the original, unmodified records. Your firm stated, without reasonable explanation, that you could not provide the requested audit trail records. When our investigators explained that your failure to provide the requested records would be documented as a refusal, you acknowledged the refusal.

Our investigators documented other instances in which your firm limited the inspection by providing some, but not all, of the records requested by the FDA investigator that FDA had authority to inspect. At multiple times during the inspection, FDA requested records of CGMP activities performed in your R&D laboratories at the behest of your quality unit. However, you limited the inspection by providing only a subset of the requested records, and our investigators also found at least one of the requested records shredded in the trash. Finally, our investigators requested chromatograms to substantiate your claim that you had identified and quantitated the impurities in **(b) (4)**, but you never provided the records that our investigators asked for to support your claim.

When an owner, operator, or agent delays, denies, limits, or refuses an inspection, the drugs may be deemed adulterated under section 501(j) of the FD&C Act. See FDA's guidance document, *Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection*, at **https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM360484.pdf (https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM360484.pdf)**.

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 acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements.

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 breaches 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.

FDA considers the expectations outlined in ICH Q7 in determining whether API are manufactured in conformance with CGMP. See FDA's guidance document, *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients,* for guidance regarding CGMP for the manufacture of API, at **https://www.fda.gov/downloads/Drugs/.../Guidances/ucm073497.pdf (https://www.fda.gov/downloads/Drugs/.../Guidances/ucm073497.pdf)**.

You are required to submit any addition, deletion, or other change to your Drug Master File to the FDA under 21 CFR 314.420. You are also required to notify each person authorized to reference the information in the DMF about pertinent changes. Failure to annually update the DMF can cause delays to FDA's review of pending applications, and may result in FDA initiating proceedings to close the DMF.

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 your facility.

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 and 99-32 on March 20, 2017.

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 continuing to refuse admission of articles manufactured at Divi's Laboratories Ltd. (Unit II) at Unit-2, Chippada Village, Visakhapatnam District 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