WARNING LETTER

Deva Holding AS - Cerkezkoy Subesi

MARCS-CMS 577493 — AUG 06, 2019

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Mr. Philipp Daniel Haas

Chairman and Chief Executive Officer

Deva Holding AS - Cerkezkoy Subesi

Halkali Merkez Mahallesi
Basin Ekspres Cd. No: 1
34303 Kucukcekmece/İstanbul
Turkey

Via UPS (mailto:Via UPS)

Issuing Office:

Center for Drug Evaluation and Research

10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

Via UPS

Warning Letter 320-19-33

Return Receipt Requested

August 6, 2019

Mr. Philipp Daniel Haas
Chairman and Chief Executive Officer
Deva Holding AS – Cerkezkoy Subesi
Halkali Merkez Mahallesi
Basin Ekspres Cd. No: 1
Kucukcekmece, 34303, Istanbul
Turkey

Dear Mr. Haas:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Deva Holding AS – Cerkezkoy Subesi at Organize Fatih Bulvar Fatih Bulvar 32 Cerkezkoy, Tekirdag, 59500, Turkey, from February 4, 2019 to February 15, 2019.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products 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 6, 2019 response in detail and acknowledge receipt of your subsequent correspondence.

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

1. **Your firm failed to perform operations related to the manufacture, processing, and packing of penicillin in facilities separate from those used for other drug products for human use (21 CFR 211.42(d)).**

You manufacture drugs on two campuses: Cerkezkoy 1 (CK1) and Cerkezkoy 2 (CK2) which are approximately ¼ mile apart. CK1 manufactures various products, including penicillin, **(b)(4)**, and non-beta-lactam drug products. You manufacture **(b)(4)** capsules for the U.S. market in the **(b)(4)** Building and penicillin drug products in an adjacent building on the CK2 campus.

A. *Penicillin cross contamination*

The presence of penicillin **(b)(4)** was detected throughout the CK2 campus outside the penicillin manufacturing areas in the campus approximately 103 times in 2017, 44 times in 2018, and 9 times in 2019 through June 2019. Of these incidents, penicillin was detected 2 times in the material acceptance ramp and 5 times in the personnel entrance area in the **(b)(4)** Building where the non-beta-lactam drug product, **(b)(4)** capsules, is made for the U.S. market. Penicillin was also detected in common areas, including dining areas, that are accessible to employees working in both the penicillin and non-penicillin manufacturing areas.

Your facility and controls to prevent contamination of non-penicillin drugs with penicillin are inadequate. Contamination of non-beta-lactam drugs with beta-lactam drugs presents great risk to patient safety, including potential anaphylaxis and death. No safe level of penicillin contamination has been determined to be a tolerable risk. Severe allergenic responses can occur in susceptible patients exposed to extremely low levels of penicillin and other beta-lactams.

In your March 6, 2019 response, you summarized your corrective actions, including the testing of retain samples from all commercial batches of **(b)(4)** capsules for penicillin contamination, using a newly-validated method, in which all batches had the result of "Not Detected". Your response also documented additional penicillin monitoring of the **(b)(4)** Building that was performed following the inspection in which no penicillin residue was detected.

Your firm's response is inadequate because your test method's limit of detection was inadequate, and your response lacks a comprehensive reassessment of the extent of contamination throughout your facility and a plan for decontamination. In addition, the beta-lactam monitoring study that was performed in the **(b)(4)** Building was inadequate because (1) it was a one-time study; (2) it only included 7 sampling locations; and (3) no sampling sites were located within the production area for the **(b)(4)** capsules.

B. *Inadequate penicillin monitoring*

Your routine, **(b)(4)** monitoring of penicillin in non-penicillin areas of your facility, conducted from January 2017 to June 2019, was inadequate because it did not include any monitoring locations within the production area where **(b)(4)** capsules are manufactured. We note that you started monitoring for penicillin in the **(b)(4)** production area after your firm was placed on Import Alert 66-40 in July 2019.

C. *Penicillin cleaning method validation*

Your firm uses **(b)(4)** solutions to decontaminate penicillin from surfaces. However, you lacked effectiveness data to show that the decontaminant solutions used throughout CK1 and CK2 are an effective decontaminant agent in your common areas, including dining areas accessible to all employees. On February 12, 2019, an employee, who performed a dissolution testing demonstration, was observed to have a stain on her clothing that was tested and determined to be **(b)(4)** after she returned from a break in the common dining area in the CK1 campus. It is unacceptable to have common areas where employees exposed to beta-lactam drugs are not isolated and separated from other employees manufacturing non-beta-lactam drugs.

Your March 6, 2019 response included additional cleaning validation studies for the **(b)(4)** solutions; however, there is no explanation as to why the original cleaning process, which utilized the same concentrations of **(b)(4)** solution, was insufficient to eliminate penicillin cross contamination which is evidenced by the findings discussed in part A.

We acknowledge your decision to recall all batches of **(b)(4)** capsules from the U.S. market due to the potential for penicillin cross contamination.

In response to this letter, provide the following:

- A plan to fully decontaminate the non-beta-lactam portion of the facility. It is profoundly difficult to completely decontaminate a facility of beta-lactam residues. If you intend to attempt decontamination so that you can resume solely non-penicillin production for the U.S market, provide a comprehensive decontamination plan.

- A list of all decontaminant solutions used in your facility, including validation data to support that the decontaminant solutions can break the beta-lactam ring of the beta-lactam drug products manufactured
- A program for future monitoring of beta-lactam residue throughout the facility
- A revised control plan for identified routes of beta-lactam contamination

For more information, see FDA's guidance document, *Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination*, at https://www.fda.gov/media/79971/download (https://www.fda.gov/media/79971/download).

2. **Your firm failed to test non-penicillin drug products for the presence of penicillin when a reasonable possibility existed that the non-penicillin drug product had been exposed to cross-contamination with penicillin (21 CFR 211.176).**

You did not test your non-penicillin drug product, **(b)(4)** capsules, for the presence of penicillin despite the known possibility of cross-contamination with penicillin.

In response to the findings of the inspection, you stated in your March 6, 2019 response that retain samples from all batches of **(b)(4)** capsules distributed to the U.S. market were tested for penicillin contamination using a newly-validated analytical method, and all batches reported a result of "not detected". However, your method for detecting penicillin in non-penicillin drugs manufactured at your facility is not sufficiently sensitive to detect very low levels of contamination. The limit of detection (LOD) for your method was reported to be **(b)(4)** mg/mL which is equivalent to **(b)(4)** parts per billion (ppb). **(b)(4)** ppb is not an acceptable LOD. Please see FDA's published analytical method which has a LOD of 0.2 ppb at https://www.ncbi.nlm.nih.gov/pubmed/29766324 (https://www.ncbi.nlm.nih.gov/pubmed/29766324).

In response to this letter, provide a commitment to either validate and implement FDA's analytical method for the analysis of penicillin in non-penicillin drug products to achieve a LOD of 0.2 ppb or validate an analytical method with a LOD that is equivalent or better than 0.2 ppb.

CGMP Consultant Recommended

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements. We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and that the consultant evaluates the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

Conclusion

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

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 on July 1, 2019.

Until you correct all violations 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 violations may also result in FDA continuing to refuse admission of articles manufactured at Deva Holding AS – Cerkezkoy Subesi, Organize Fatih Bulvar Fatih Bulvar 32 Cerkezkoy, Tekirdag, 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 violations 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:

Carrie Ann Plucinski

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 3009864318.

Sincerely,

/S/

Francis Godwin

Director

Office of Manufacturing Quality

Office of Compliance

Center for Drug Evaluation and Research

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