Attix Pharmaceuticals 6/22/15

Department of Health and Human Services

Public Health Service
Food and Drug Administration

Silver Spring, MD 20993

Warning Letter

WL: 320-15-11

CERTIFIED MAIL

RETURN RECEIPT REQUESTED

June 22, 2015

Mr. Syveon D. Liu
CEO & Owner

Attix Pharmaceuticals

184 Front St. East, Unit 801

Toronto, ON, M5A 4N3

Canada

Dear Mr. Liu:

We inspected your pharmaceutical manufacturing (repackaging) facility, Attix Pharmaceuticals, 184 Front St. East, Unit 801, Toronto, Ontario, Canada, from November 10, 2014, through November 14, 2014. Our investigator from the U.S. Food and Drug Administration (FDA) identified significant deviations from current good manufacturing practice (CGMP) for the manufacture of active pharmaceutical ingredients (APIs).

These deviations cause your APIs to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 351(a)(2)(B), in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We reviewed your firm's response dated December 3, 2014, in detail. It lacks sufficient corrective actions.

Our investigator observed specific deviations during the inspection, including, but not limited to, the following:

1. Failure to package beta-lactam drug products, (including penicillin and non-penicillin beta-lactams) and other drug products under appropriate conditions to avoid potential cross-contamination.

a. Your firm failed to use separate facilities to manufacture penicillins, non-penicillin beta-lactams, and non-beta-lactam APIs.

i. According to your Repackaging Logbook, on February 27, April 23, July 8, and July 22, 2014, you packaged a number of beta-lactams, including **(b)(4)**, in a facility that is not dedicated to manufacturing beta-lactam drugs.

ii. You did not use dedicated equipment (for example, hoods) or air handling systems to prevent cross-contamination.

b. Your firm increased the risk of cross-contamination by allowing personnel and materials to move freely between beta-lactam and non-beta-lactam manufacturing areas.

These practices create an unacceptable risk of beta-lactam cross-contamination in other beta-lactams and in non-beta-lactam APIs.

During the inspection, you stated that you ceased penicillin operations. However, you manufacture other beta-lactam products beyond penicillin, so ceasing penicillin operations is inadequate to address non-penicillin beta-lactams. You should take similar efforts to mitigate the risks of cross-contamination by non-penicillin beta-lactams, because they pose similar risks to patients.

In your response, you described your operation in detail. **(b)(4)** is repackaged under high-efficiency particulate air (HEPA) filtered hoods. In an attempt to reduce direct contamination, you use **(b)(4)** on the work surface to collect spillage. Between repackaging operations, you clean the hoods **(b)(4)** times with **(b)(4)**.

Your response is insufficient because it fails to mitigate the high risk of cross-contamination while packaging powder beta-lactams in a shared facility. You also did not include a scientifically sound justification for using **(b)(4)** to inactivate beta-lactam rings on surfaces.

Cleaning cannot substitute for proper segregation. Cross-contamination with your sensitizing agents can initiate life-threatening allergic reactions or other drug-induced hypersensitivity reactions. Your current practices demonstrate an unacceptably high risk of beta-lactam cross-contamination into other APIs packaged at your facility. You should conduct all beta-lactam manufacturing activities in dedicated, segregated facilities with separate air handling systems and production equipment.

No safe level of penicillin contamination has been determined to be a tolerable risk. Severe allergenic response can occur in susceptible patients exposed to extremely low levels of penicillin and other beta-lactams. Such levels are difficult to detect with current analytical methods.

We recommend that you retrospectively assess whether any of the non-beta-lactams packaged by your firm were contaminated with beta-lactams. However, please be mindful that any test intended to detect beta-lactam contamination provides only limited confidence due to method limitations and sample size. This low detectability, the severity of risk to patients, and the limitations of production controls to preclude cross-contamination underscore the importance of meeting the minimum standard of manufacture in completely separated facilities.

For additional information, please refer to the guidance for industry, “Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination,” available at **http://www.fda.gov/downloads/Drugs/Guidances/UCM246958.pdf**

As indicated above, although you discontinued repackaging penicillin, you continue to repackage beta-lactam and non-beta-lactam products. Indicate how you will assure that drugs manufactured at your facility following your discontinuation of penicillin repackaging will be free from beta-lactam contamination. In your response to this letter include your plans for decontaminating, renovating, and requalifying your facility. Include decontamination

agent(s), your analytical methodology for environmental testing, your acceptance criteria, and the studies you used to support your decontamination plan.

In your response to this letter, if you continue to repackage any beta-lactam products, submit your comprehensive plan for complete segregation of these products from non-beta-lactams. Furthermore, include your proposed action plan to address the hazards posed by any drugs with potential beta-lactam contamination.

2. Failure to transfer expiry dates received from the API manufacturer to your customers.

During our inspection, we reviewed your internal audit from September 2014. You identified 186 instances when your firm inaccurately transferred quality information (manufacturer-assigned expiry dates) to your customers. Expiry dates on your certificates of analysis (CoAs) exceeded the manufacture's assigned expiry/retest dates by up to **(b)(4)**. You provided no scientific justification to extend the expiry dates.

a. **(b)(4)**, lot #**(b)(4)**, expiry date **(b)(4)**. The original manufacturer's expiry date was February 16, 2015.

b. **(b)(4)**, lot #**(b)(4)**, expiry date **(b)(4)**. The original manufacturer's expiry date was August 20, 2014.

According to your response, personnel responsible for this practice are no longer employed by your company. You have trained your staff in the required standard operating procedure. However, you failed to specify whether all data you transferred on your CoAs, including data compiled by former employees, has been retrospectively evaluated for accuracy and completeness. In your response to this letter, describe how you will determine the effectiveness of your corrective actions.

Deviations cited in this letter are not intended as an all-inclusive list of deviations at your facility. You are responsible for investigating and determining the causes of the violations identified above, for preventing their recurrence, and for preventing other violations.

Because of the CGMP issues at your firm, we urge you to engage a third party consultant with appropriate CGMP expertise to assess your firm's facility, procedures, processes, and systems to ensure that the APIs you repackage and distribute have appropriate safety, identity, strength, quality, and purity.

Until you complete all corrections, and FDA has confirmed that deviations are corrected and your firm complies with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as an API manufacturer.

In addition, until your manufacturing practices are verified to comply with CGMP, your firm will remain under FDA Import Alert 66-40. FDA will continue to refuse admission of articles manufactured at Attix Pharmaceuticals, 184 Front St. East, Suite 801, Toronto, Canada, into the United States, under Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3).

Articles may be subject to refusal of admission pursuant to Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3), 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 Act, 21 U.S.C. 351(a)(2)(B).

Within 15 working days of receipt of this letter, notify this office, in writing, of the specific steps that you have taken to correct deviations and prevent recurrence. Include copies of supporting documentation.

If you cannot complete corrective actions within 15 working days, state the reason for the delay and the date by which you will have completed the corrections. If you no longer manufacture the APIs at issue, provide the date(s) and reason(s) you ceased production. Send your reply to:

Mary D. Davis-Lopez, Compliance Officer

U.S. Food and Drug Administration

Center for Drug Evaluation and Research

Office of Manufacturing Quality

Division of Drug Quality II

White Oak Building 51 Room 4312

10903 New Hampshire Avenue

Silver Spring, Maryland 20993

Please identify your response with FEI # 3008197162.

Sincerely,

/S/

Thomas J. Cosgrove, J.D.

Director

Office of Manufacturing Quality

Office of Compliance

Center for Drug Evaluation and Research