SmithKline Beecham Limited 6/30/16

Department of Health and Human Services

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

Via UPS
320-16-21
Return Receipt Requested

Warning Letter:

June 30, 2016

Sir Andrew Witty
Chief Executive Officer
SmithKline Beecham Limited
GSK House
980 Great West Road
Brentford
MIDDLESEX
TW8 9GS
UNITED KINGDOM

Dear Sir Andrew:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, SmithKline Beecham Limited at Clarendon Road, Worthing, United Kingdom from July 2–10, 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 firm's July 31, 2015, response in detail and acknowledge receipt of subsequent responses.

Our investigators observed specific deviations including, but not limited to, the following.

1. Failure to have appropriate procedures (or practices) in place to prevent cross-contamination from dedicated penicillin manufacturing area to non-dedicated areas.

A. Penicillin cross contamination

We documented findings of penicillin in non-penicillin manufacturing areas approximately 69 times in 2012, 72 times in 2013, 30 times in 2014, and 16 times through July 7, 2015. Your facility and controls to prevent contamination of non-penicillin drugs with penicillin are wholly inadequate.

Contamination of non-beta-lactam drugs with beta-lactam drugs presents great risks to patient safety, including anaphylaxis and death. 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. Due to the limitations of sampling and current analytical test methods, such levels are very difficult to detect.

We acknowledge your decision to **(b)(4)** until completion of a product quality risk assessment. Your firm also recalled various lots of Bactroban® (mupirocin calcium) products because of potential contamination with penicillin and foreign substances such as glass, paint fragments, and fibers.

In your response, you committed to revalidating your penicillin decontamination method. Your response is inadequate because it lacks a comprehensive reassessment of the extent of contamination throughout your facility, a gap analysis of previous decontamination efforts, and a copy of your new decontamination plan.

B. Penicillin detection method validation

Your method for detecting penicillin in non-penicillin drugs manufactured at your facility is not validated to detect the different types of penicillin manufactured at your facility. In addition, you could not locate the raw data for the method validation. Your firm has changed the method since the original validation.

C. Penicillin cleaning method validation

Your firm uses **(b)(4)** to decontaminate penicillin from all surfaces. However, the cleaning validation only demonstrated **(b)(4)** to be effective in the removal of **(b)(4)**. Your firm discontinued manufacturing **(b)(4)** in **(b)(4)**. You have not updated your cleaning validation and have not demonstrated whether the method originally used for **(b)(4)** is also effective for the penicillin drugs you manufactured at the time of our inspection.

In your response, you acknowledged the problems with your current analytical method and its validation. Your response is inadequate. You did not provide supporting data or justification for your cleaning validation.

In response to this letter, commit to one of the following two options for the building you have used to manufacture penicillin.

- Dedicate the facility to penicillin only: We strongly urge you to dedicate the facility to penicillin-only production. If you intend to dedicate the facility to penicillin-only production, provide your timeline for implementation. Also indicate the controls you have implemented to prevent any non-penicillin drugs previously manufactured at this facility from entering the U.S. supply chain.
- Fully decontaminate 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 API production for the U.S. market, provide a comprehensive decontamination plan. Also update your methods for detection of penicillin and address all potential sources of cross-contamination of penicillin into non-penicillin drugs. Until FDA determines that your proposed decontamination plan, methods, and procedures are adequate, comprehensively implemented, and verified via an FDA inspection, you should not introduce any non-penicillin drugs into the U.S. supply chain.

For more information, see FDA's guidance document, *Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination*, at http://www.fda.gov/downloads/Drugs/.../Guidances/UCM246958.pdf.

2. Failure to adequately investigate critical deviations and implement corrective and preventive actions.

*A. Microbial contamination in **(b)(4)** water systems*

From April 20, 2014, to February 17, 2015, you investigated at least 25 breaches of the alert level (**(b)(4)** colony forming units) or action level (**(b)(4)** colony forming units) for microbial contamination in your water system loops in Building **(b)(4)**. You used water produced from this system to manufacture **(b)(4)** API. Of note, you identified *Burkholderia cepacia*, a waterborne organism known to contribute to biofilm formation in water systems, in several of your alert-level and action-level investigations.

Your investigations failed to adequately establish root causes. In 16 of the 25 investigations, you concluded that the root cause was sampling error but had no supporting evidence. You did not determine a root cause in the remaining nine investigations. Our inspection also found that you were not sanitizing the **(b)(4)** water system loops **(b)(4)**, as required in your procedure *PAA219 Operation & Maintenance for **(b)(4)** Plant **(b)(4)** Water System*.

In your response, you acknowledged that your **(b)(4)** water system investigations were not robust. However, you made no commitment to conduct a comprehensive investigation into the breaches and overall adverse trends.

In response to this letter, provide a summary report of your reassessment and remediation of **(b)(4)** your **(b)(4)** water systems. Also include sampling use points and sampling schedules.

*B. **(b)(4)** API batch **(b)(4)** with out-of-specification bioburden*

Our investigators found that three of the **(b)(4)** of **(b)(4)** (batch **(b)(4)**) had bacterial counts (bioburden) exceeding your specification. **(b)(4)** had more than **(b)(4)** colony forming units of *Sphingomonas paucimobilis* per milliliter of product. *Sphingomonas paucimobilis*, an opportunistic pathogen, is one of the organisms you identified in the water system used to manufacture this batch. Notably, *Sphingomonas paucimobilis* was also found in **(b)(4)**, but this **(b)(4)** was released based on passing microbial count testing.

Following an investigation, your firm elected to reject the **(b)(4)** that failed microbiological quality control testing. However, microbial contamination by its nature rarely occurs uniformly. Therefore, rejecting the specific **(b)(4)** that failed final QC testing, while releasing the remaining **(b)(4)**, may not prevent exposure of customers to potentially objectionable contamination.

In your response, you attributed the high bioburden root cause to an extended **(b)(4)** hold time. Your response is inadequate. Your firm has no established maximum **(b)(4)** hold time. You failed to include any supporting data to correlate your **(b)(4)** holding times with increased API bioburden. You did not extend your investigation into the **(b)(4)** other **(b)(4)** with similar or longer **(b)(4)** hold times.

In response to this letter, include a reassessment of your water system and how it may contribute to high API bioburden. Also provide your corrective action and preventive action plan to prevent recurrence.

*C. Foreign particles found in **(b)(4)** API **(b)(4)***

Your investigation into foreign particles found in **(b)(4)** batch **(b)(4)** identified:

- green fibers consistent with scouring pads
- red flakes consistent with paint in the manufacturing plant
- black particulates consistent with glass particles

You concluded that these were “acceptable intrinsic” contaminates.

Your response is inadequate. It failed to include a root-cause evaluation of glass particles and the foreign materials found in these drugs. You also failed to evaluate the impact of the contaminants on all other drugs manufactured with the same equipment in the same facility.

In response to this letter, provide a risk assessment for the **(b)(4)** manufacturing process and other drugs produced with the same equipment. Include an evaluation of the physical condition of your facility and of your cleaning and preventive maintenance procedures for your manufacturing equipment.

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 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.

After you receive this letter, you have 15 working days to respond to this office in writing. Specify what you have done to correct your deviations and to prevent their recurrence.

If you cannot complete corrective actions within 15 working 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 drug manufacturer. Failure to correct these deviations may also result in FDA refusing admission of articles manufactured at SmithKline Beecham Limited, Clarendon Road, Worthing, United Kingdom, 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:

Rafael Arroyo
Compliance Officer
U.S. Food and Drug Administration
White Oak, Building 51, Room 4235
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 1000166776.

Sincerely,
/S/
Francis Godwin
Acting Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

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