Inspections, Compliance, Enforcement, and Criminal Investigations

SmithKline Beecham (Cork) Ltd. 3/18/14

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

Warning Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL: 320-14-06

March 18, 2014

Sir Andrew Witty
CEO
GlaxoSmithKline
5 Moore Drive
Research Triangle Park, NC 27709

Dear Sir Andrew:

During our October 18-23, 2013 inspection of your pharmaceutical manufacturing facility, SmithKline Beecham (Cork) Ltd., located at Currabinny, Carrigaline, Cork, Ireland, investigator (s) from the U.S. Food and Drug Administration (FDA) identified 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 have conducted a detailed review of your firm's response and note that it lacks sufficient corrective actions.

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

1. Failure to fully investigate critical deviations.

Your firm discovered that the **(b)(4)** used to manufacture **(b)(4)** batches of **(b)(4)** and **(b)(4)** batches of **(b)(4)** was contaminated with material from your pharmaceutical waste tank, which contained APIs, intermediates, and solvents. Examples of chemicals that are collected in the waste tank include **(b)(4)**. Your firm became aware of this contamination in January 2012 and completed risk assessments to determine the impact on the quality of **(b)(4)** manufactured using the contaminated solvents on April 19, 2013. Your firm distributed **(b)(4)** shipments of **(b)(4)** potentially contaminated **(b)(4)** batches after becoming aware of this significant deviation. In contrast, **(b)(4)** batches made with the contaminated **(b)(4)** were rejected.

Quality impact assessments were made for both **(b)(4)** and **(b)(4)**, but we note that the approach taken in the two assessments was different. For instance, the **(b)(4)** assessment noted that the standard release testing did not detect significant quantities of contaminants in the potentially impacted **(b)(4)** batches, but that additional testing on **(b)(4)** from **(b)(4)** showed the impacted batches were exposed to significant amounts of **(b)(4)**. The assessment states that the sample preparation used in the **(b)(4)** sample release testing appears to be incapable of complete extraction of the potential contaminants, and it therefore relied on results obtained from the additional testing from the **(b)(4)** of **(b)(4)** product to demonstrate that the **(b)(4)** batches were impacted by the pharmaceutical waste contamination event. Your firm's assessment for **(b)(4)** included no such additional testing and relied on the **(b)(4)** samples' passing test results, concluding that there was no quality impact to the **(b)(4)** batches.

Your firm's SOP regarding communication of significant deviations states that your firm must communicate to the receiving site information concerning deviations having a potential quality impact on the product. During the inspection, your personnel informed our investigator that your firm determined that there was no potential to impact the quality of the affected products manufactured with **(b)(4)** and chose not to "escalate" the deviation by notifying your customers. We are concerned that your firm does not consider the entry of pharmaceutical waste streams into your manufacturing process a significant deviation with a potential quality impact. In your response to the Form FDA-483, you acknowledged that you should have informed your customers of this incident; however, you did not describe any recent or future communication with your customers regarding the incident to rectify the prior lapse.

In your response to this letter, please address the concerns outlined above. Please also describe why the quality assessments appear to assume uniform distribution of contaminants following addition of **(b)(4)** to the waste stream and before the backflow of contaminants into the **(b)(4)** tank. Provide a revised quality assessment for **(b)(4)** that clearly describes all calculations used to support the conclusions, and clearly describe any altered conclusions after addressing the issues described in this letter. For each analytical method used to support your conclusions, provide method qualification information, including the limit of detection for each potential contaminant. Also, provide a quality impact assessment for your **(b)(4)** product, which was also manufactured using **(b)(4)** around the time of the initial contamination in the **(b)(4)** tank. Describe any contact you have had with the customers of the potentially affected products and your plans with respect to the disposition of any potentially affected batches that remain within expiry.

2. Failure to investigate and document out-of-specification results.

Your firm tested solvent from the **(b)(4)** tank in September 2011 and October 2011 to look for potential **(b)(4)** contamination via a gas chromatographic method. The chromatograms from both samples show large peaks for **(b)(4)** as well as small but detectable levels of at least ten other contaminants. These unexpected peaks should have indicated to your firm that the **(b)(4)** tank had been contaminated with pharmaceutical waste, as described above. Instead, your laboratory personnel ignored these unexpected peaks and conducted no investigation into what gave rise to them. As a result, your firm did not notice the **(b)(4)** tank contamination until a third sample from the tank was tested in January 2012.

In your response to the Form FDA-483, you stated that there was no reason to expect **(b)(4)** contamination and therefore the analyst did not notice the **(b)(4)** peak. Your response does not address why the analyst did not notice the numerous other detected contaminants in the chromatogram, nor did it address why a second reviewer did not notice the unexpected peaks in the chromatograms. Please address these issues in your response to this letter. In addition, please explain why the **(b)(4)** testing sample from the tank was collected in November 2011 and was not tested until January 2012, and provide supporting documentation from the method validation describing the stability of the tank samples during this lengthy storage period.

3. Failure to demonstrate that your manufacturing process can reproducibly manufacture an API meeting its predetermined quality attributes.

Your firm's validation protocol for **(b)(4)** states that a minimum of three consecutive pre-nominated process performance qualification (PPQ) batches were to be produced to demonstrate initial process validation. However, your firm was unable to produce three consecutive successful batches due to **(b)(4)** during the production of multiple batches and therefore re-nominated the PPQ batches on two different occasions. Your firm made modifications to the equipment used in manufacturing after noticing **(b)(4)** during the first two batches manufactured, but these changes were not sufficient to prevent further **(b)(4)** during the fifth batch. Following the fifth batch, your firm replaced the**(b)(4)** used in the manufacturing process and produced a sixth batch. During the execution of the validation protocol, the originally "pre-nominated" PPQ batches that were rejected due to **(b)(4)** were assigned for reprocessing.[1] Based on manufacture of the third, fourth, and sixth batches without this processing problem, your firm considered the process validation protocol to be successfully executed.

The process performance qualification studies described above suggest that your equipment has not been sufficiently demonstrated to reliably perform its intended function, namely **(b)(4)** and **(b)(4)** of the **(b)(4)** from the process stream. Demonstrating suitability of equipment used in the manufacturing process is a fundamental element of establishing the state of control of your process. Because of these equipment suitability deficiencies, we are concerned that your firm has not adequately demonstrated an ability to consistently and reproducibly manufacture **(b)(4)** without **(b)(4)**.

In your response to this letter, please provide justification for the selection of non-consecutive batches during the execution of your validation protocol. Describe any revisions to your validation SOP to clarify under what specific circumstances "re-nomination" of PPQ batches would be considered acceptable. Provide any additional evidence of your firm's ability to reproducibly manufacture **(b)(4)** without **(b)(4)** and while meeting all critical quality attributes. Specifically, provide the entire batch manufacturing history for **(b)(4)** following batch **(b)(4)**, noting any other incidents of **(b)(4)** problems.

The deviations cited in this letter are not intended to be an all-inclusive list of deviations that exist at your facility. You are responsible for investigating and determining the causes of the deviations identified above and for preventing their recurrence and the occurrence of other deviations.

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of finished drug products or active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Program immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov so that we can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Program also allows you to meet any obligations you may have to report discontinuances in the manufacture of your drug under 21 U.S.C. 356C(a)(1), 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. In appropriate cases, you may be able to take corrective action without interrupting supply, or to shorten any interruption, thereby avoiding or limiting drug shortages.

Until all corrections have been completed and FDA has confirmed corrections of the deviations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as an API manufacturer. In addition, your failure to correct these deviations may result in FDA refusing admission of articles manufactured at SmithKline Beecham (Cork) Ltd., Currabinny, Carrigaline, Cork, Ireland into the United States under Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3). The 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 fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct and prevent the recurrence of deviations, and

provide copies of supporting documentation. If you cannot complete corrective actions within fifteen working days, state the reason for the delay and the date by which you will have completed the corrections. Additionally, if you no longer manufacture or distribute the APIs at issue, provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 1000170338.

Please send your reply to: Mary Farbman, Ph.D., Consumer Safety Officer; 10903 New Hampshire Avenue; Building 51 Room 4234; Silver Spring, MD 20993-0002.

Sincerely,
/S/
Steven Lynn
Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

cc: Finbar Whyte
Site Director
GlaxoSmithKline (GSK)
Carrabinny, Carrigaline
Cork, Ireland

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