U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration



## Inspections, Compliance, Enforcement, and Criminal Investigations

### SmithKline Beecham Limited 10/7/11

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

**Warning Letter**

**VIA UPS MAIL**

**WL: 320-12-01**

October 7, 2011

Mr. Joseph C. Foley
Interim Director
SmithKline Beecham Limited
Worthing West Sussex
BN14 8QH, United Kingdom

Dear Mr. Foley:

During our March 2011 inspection of your pharmaceutical manufacturing facility, SmithKline Beecham Limited located in Worthing West Sussex, United Kingdom, investigators from the Food and Drug Administration (FDA) identified significant violations of Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your drug products 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 reviewed your firm's response of April 7, 2011, and note that it lacks sufficient corrective actions.

Specific violations observed during the inspection include, but are not limited, to the following:

1. Your firm has not established appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 C.F.R. § 211.113(b)]. For example:

a. The qualification of your disinfectant **(b)(4)** failed to demonstrate that it is suitable and effective to remove microorganisms from different surfaces. Specifically, this disinfectant failed to meet qualification criteria when challenged with multiple organisms.

Your disinfectant qualification for **(b)(4)** and **(b)(4)** bi-spore disinfectants documented that the log reduction criteria (Bacteria ≥ 4, Fungi ≥ 3) was not met when challenged with multiple organisms in a variety of surfaces. After disinfection, you recovered Micrococcus luteus on vinyl, **(b)(4)**, stainless steel, glass, and wall laminate and *Enterobacter cloacae, Rhodococcus sp, Burkholderia cepacia, Pseudomonas aeruginosa, Methylobacterium mesophilicum and, Acinetobacter lwoffi* on glass. However, your procedures for routine cleaning of the aseptic manufacturing area continue to require the use of unqualified disinfectants during days **(b)(4)** through **(b)(4)** of your disinfectant program.

Your firm's response indicates that the failure to meet the log reduction criteria was due to the test conditions and not the efficacy of the disinfectant. However, you did not include documentation to support this conclusion. Moreover, your firm submitted an updated Technical Report (LT8R1310) "Interim Report for the Disinfectant Validation Study of the **(b)(4)** and **(b)(4)** Performed by **(b)(4)**", signed by your Quality Assurance (QA) on July 27, 2011, indicating that the disinfectant **(b)(4)** has been unable to comply with the three-log reduction for *Micrococcus* luteus microorganism on some surfaces.

b. Procedure SOP PMC6169 "Aseptic & Support Area Sanitization Following Maintenance Shutdown" is inadequate.

A media fill conducted during January 2011 resulted in two contaminated units. Your firm attributed the failures to stopper bags left inside the class 100 area for a long period of time (throughout a shutdown that took place prior to the media fill in January 2011 shutdown). There is inadequate information available to support your conclusion, including information regarding the microorganisms recovered from the stopper bags and the sterility test conducted, along with an evaluation of your sampling procedure and environmental monitoring program.

Significantly, your firm had intended to use the media fill data to extend the sterility holding times for product contact components, without the approval of your Quality Unit. We also are concerned that your SOP PMC6169 did not require manufacturing materials to be removed to an appropriate area for storage during shut-down of operations and prior to bringing the area back into classified status.

c. Personnel gown monitoring conducted during routine aseptic filling of **(b)(4)**g (**(b)(4)**cc and **(b)(4)**cc) and **(b)(4)**g (**(b)(4)** cc) is inadequate.

The inspection documented that your firm conducts personnel monitoring on a **(b)(4)** basis and upon **(b)(4)** the classified manufacturing rooms by only sampling the hood, goggles, and sleeves. We are concerned about your current gowning monitoring approach as operators may perform substantial interventions into the Restricted Access Barriers (RABs), where sterile product is exposed, several times per week. In addition, the investigators noticed during the inspection one of the operators sanitizing his hands with **(b)(4)** immediately prior to conducting his own personnel monitoring sampling. Your personnel monitoring program should include appropriate sampling and practices to reflect whether personnel maintain asepsis during sterile drug manufacture.

In your response to this letter, please provide a detailed description of the controls implemented to ensure operators that enter the class 100 (ISO 5) area are sampled adequately in the "QA Grade B Room" (ISO 6). Also provide this same information for operators who enter the aseptic processing room for non-aseptic filling activities. Please include your rationale for these monitoring schedules.

In addition, the **(b)(4)**") Dynamic Airflow Visualization" video provided in your firm's response shows an operator spraying his hands with **(b)(4)(b)(4)(b)(4)**% directly over the air viable microbial plate. This practice is unacceptable because the environmental monitoring results from plates sprayed with ) **(b)(4)**% may be inaccurate and may not reflect the actual microbiological environment of the Class 100 (ISO 5) room.

2. Your firm fails to follow laboratory control procedures [21 C.F.R. § 211.160(a)]. For example:

The inspection revealed that the laboratory investigations FQ991_6058, FQ991_6239, FQ991_7049, FQ991_7050, and FQ991_7484 were conducted without having Form B completed and approved by your Quality Unit, as required by your procedure. Your firm's procedure QAA4 "Investigation Out of Specification (OOS) Test and Atypical Results Procedure" establishes that the Form B is intended to document any retest, root cause investigation, and whether any remedial corrective and preventative actions are required.

Your firm's response indicates that although the Form B was not used, the quality of the investigations is equivalent to those investigations in which the Form B was completed. However, you provided no support for this conclusion. In addition, your response failed to justify the re-test that was conducted without authorization by your Quality Unit.
In response to this letter, please review all the OOS investigations for product within expiration date to determine if the investigation procedures were properly followed, and include any re-test analyses conducted without the approval of your Quality Unit. Please provide a list of the investigations evaluated, and a summary of each investigation's outcome.

3. The quality control unit does not adequately exercise its responsibilities to approve procedures or specifications that may impact the identity, strength, quality, and purity of the drug product [21 C.F.R. § 211.22(c)]. For example:

The inspection documented that the visual inspection certification program (VIC) for **(b)(4)**g ((**b)(4)**cc and **(b)(4)**cc) and **(b)(4)**g ((**b)(4)**cc) finished product does not adequately challenge the technician(s) performing the inspection. The visual inspection competency (VIC) program only requires that **(b)(4)** of the five critical defects be included in the challenge set. Although the following are identified as critical defects: a vial with a crack neck, missing cap, missing stopper, high/low weight, and a foreign body, only a missing cap defect is included in the visual inspection program. This test will only show that the technician(s) is capable of detecting a missing cap, but it does not show that the technician is capable of detecting other critical defects. Additionally, the SOP does not require that the critical defect challenge vial selected be rotated to ensure that each inspector is challenged to detect each critical defect.

In the response to this letter, please indicate what specific steps you have taken to ensure that all distributed lots are properly evaluated for all critical defects.

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations. If you wish to continue to ship your products to the United States, it is the responsibility of your firm to ensure compliance with all U.S. standards for CGMP and all applicable U.S. laws and regulations.

Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. In addition, failure to correct these violations may result in FDA refusing admission of articles manufactured at SmithKline Beecham Limited, Southdown View Way, Worthing West Sussex, BN14 8QH, United Kingdom into the United States. The articles are 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 Current Good Manufacturing Practice 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 violations. Include an explanation of each step being taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Please identify your response with FEI #1000166776.

If you have questions or concerns regarding this letter, contact Rafael Arroyo, Compliance Officer, at the below address and telephone number.

U.S. Food and Drug Administration
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Sincerely,
/Teddi Lopez/
Teddi Lopez on behalf of Steven Lynn
Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

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