U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Bristol Myers Squibb Holdings Pharma., Ltd.

Department of Health and Human Services

Public Health Service
Food and Drug Administration
466 Fernandez Juncos Avenue
Puerta De Tierra
San Juan, Puerto Rico 00901·3223

WARNING LETTER
10-SJN-WL-06

August 30, 2010

CERTIFIED MAIL RETURN
RECEIPT REQUESTED

Mr. Jim Cornelius
Chairman and CEO
Bristol-Myers Squibb Company
345 Park Avenue
New York, NY 10154

Dear Mr. Cornelius:

During our March 17-31, 2010 inspection of your manufacturing facility, Bristol-Myers Squibb Holding Pharma Ltd., located in Manati, Puerto Rico, 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 (C.F.R.), 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 dated April 14, 2010, 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 or followed 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 operators at your facility have repeatedly failed to comply with your procedures for aseptic operations. Specifically, your operators have been observed to not comply with Standard Operating Procedure (SOP) **(b)(4)** for ex. Operators did not follow SOP requirements pertaining to interventions into the Class 100 (ISO 5) zone.

Our review indicates that there are on-going problems with your personnel failing to comply with procedures. In your response, you state that your SOPs are inadequate and do not reflect actual practices. While you commit to revising your SOPs, it is FDA's expectation that your firm promptly correct all deficient procedures to ensure employees do not continue improper practices.

To ensure quality of the drug product in aseptic operations, your personnel must employ strict discipline as they comply with adequate and appropriate procedures. We acknowledge your response stating that supervisors will monitor the performance of the aseptic operators on a daily basis. Please provide more information on the extent of this supervision. Also, your response is inadequate because the use of a log book to document supervisory observation of the aseptic filling process does not provide assurance of adequate supervision. Please provide a plan that evaluates your training program, specifically the program's effectiveness and your assurances of personnel compliance to aseptic processes prior to certification to work in an aseptic area.

b. Your firm failed to design and perform an adequate aseptic process simulation (i.e., media fill) based upon the same controls used for routine production. We note that the **(b)(4)** was observed **(b)(4)** during actual production. However, this intervention was performed only once during the media fill in 2009.

In your response, you state that you have amended your SOP **(b)(4)** to ensure that the media fill simulation maintains alignment with routine aseptic filling processes.

During aseptic operations, it is critical that your Quality Control Unit (QCU) has reviewed routine aseptic filling processes prior to the preparation of the aseptic process simulation protocol and that the new media fills include all appropriate interventions.

This is a repeat observation from our 2005 and 2009 inspection.

2. Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed [21 C.F.R. § 211.192].

For example, your firm has failed to thoroughly investigate the recurrence of environmental excursions in your facility and has failed to verify the effectiveness of prior corrective actions that addressed similar environmental excursions. Specifically, you reported **(b)(4)** environmental samples, described as, **(b)(4)** from January to February 2010 for the Class 100 (ISO Grade 5) areas. These **(b)(4)** environmental excursions were not investigated by your firm.

Previously, you documented approximately **(b)(4)** environmental excursions (September 9 to November 19, 2009) as **(b)(4)** associated with **(b)(4).** As part of your investigation **(b)(4)** (opened on October 26, 2009), the activities and interventions conducted in the aseptic core area from September to November 2009, were evaluated. Your firm implemented corrective actions as a result, including personnel training in the areas of gowning inspection, aseptic techniques, and cleaning procedures.

In your response, you state that the environmental excursions were from non-product contact areas and had no adverse product impact. We disagree with this premise because many of the **(b)(4)** sample locations (e.g., **(b)(4)**) were in the class 100 (ISO Grade 5) room used to load and unload lyophilizers. Your data demonstrates that this area is prone to contamination by the aseptic area personnel loading and unloading the lyophilizers, which is a manual operation. Manual operations represent a higher risk and additional measures may be required to ensure that an appropriately controlled environment is utilized to manufacture drug products purporting to be sterile.

In addition, your investigation of gown quality does not provide assurance that your clean room gown supplier has implemented appropriate actions to prevent a reoccurrence of defective gowns being used in your clean rooms. It is your responsibility to ensure that your clean room gown supplier has adequate inspection procedures to remove damaged gowns from your clean room gown supply. There is no mention in your investigation of a decision to shorten the life span of gannents, supplied to your firm, to prevent the excessive wear found during your investigation.

3. Your firm has not established scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity [21 C.F.R. § 211.160(b)].

For example, your Firm established acceptance criteria for major defects in the control Form entitled, "Working Inspection Qualification, WIQ," using **(b)(4).** The acceptance criteria is inadequate because your QCD approved the specification without adequate justification or a scientifically sound statistical analysis.

Your response is inadequate because you fail to provide a sound scientific rationale for either establishing your acceptance criteria or classifying defects upon visual inspection of your lyophilized products. Typically, vials, with glass particles and cracks, are considered critical defects. However, you have classified these defects as major defects without justification.

The violations cited in this letter are not intended to be an all-inclusive statement of the 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, as well as occurrence of other violations. It is your responsibility to ensure that your firm complies with all requirements of federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of pending drug applications listing your facility, until the above violations are corrected. FDA may re-inspect to verify corrective actions have been completed.

Repeat citations from prior inspections indicate that your quality control unit is either not appropriately exercising its responsibilities or does not have the authority to carry out its responsibilities. Due to continuing CGMP issues at your firm, we recommend you engage a third party consultant having appropriate CGMP expertise to assess your firm's facilities, procedures, processes, and systems to ensure that your drug products have their appropriate identity, strength, quality, and purity.

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. Additionally, your response should state if you no longer manufacture or distribute the drug product(s) manufactured at this facility, and provide the date(s) and reason(s) you ceased production.

Your reply should be sent to the following address: Food and Drug Administration, Attention: Margarita Santiago, Compliance Officer, 466 Fernandez Juncos Avenue, San Juan, Puerto Rico 00901-3223. If you have any questions concerning the violations noted please contact Ms. Santiago at (787) 474-4789 or by electronic mail at margarita.santiago@fda.hhs.gov.

Sincerely,
/S/
Maridalia Torres
District Director
San Juan District

cc: Mrs. Ivonne Lassalle
Vice-President & General Manager
Bristol-Myers Squibb Holding Pharma, Ltd
P.O. Box 30100
Manati, PR 00674-3000

Ms. Roberta L. McKee, Senior Vice President Americas, Asia Pacific Drug Products Operations and Ms. Donna Gulbinski, Senior Vice President Worldwide Quality & Compliance
P.O. Box 191
New Brunswick, NJ 08903-0191

Links on this page: