Inspections, Compliance, Enforcement, and Criminal Investigations

Boehringer Ingelheim Pharma GMBH & Co 5/6/13

Department of Health and Human Services

Public Health Service
Food and Drug Administration

Warning Letter

WL: 320-13-015

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

May 6, 2013

Dr. Gerhard Gigl
Senior Vice President
Boehringer-Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

Dear Dr. Gigl:

During our November 5-12, 2012 inspection of your active pharmaceutical ingredient (API) and finished pharmaceutical manufacturing facility, Boehringer-Ingelheim Pharma GmbH & Co. KG., located at D-55216 Ingelheim am Rhein, Germany, investigator(s) from the U.S. Food and Drug Administration (FDA) identified significant violations of current good manufacturing practice (CGMP) for the manufacture of APIs and the CGMP regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your APIs and drug product(s) 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 dated November 30, 2012 and note that it lacks sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondence dated January 31, 2013, February 28, 2013, and March 28, 2013.

Our investigator(s) observed specific violations during the inspection, including, but not limited to, the following:

API: CGMP VIOLATIONS

1. Failure of your Quality Unit to thoroughly investigate critical deviations in the manufacturing of your active pharmaceutical ingredient (API).

For example, your firm did not conduct a thorough investigation to determine the source of foreign particles in your **(b)(4)** active pharmaceutical ingredient, (API) nor did you implement timely and appropriate corrective and preventive actions.

The foreign particles found in your **(b)(4)** included **(b)(4)**. Your firm’s response acknowledges that while reports of the presence of foreign particles were observed in batches produced in

2009, all of the batches in the campaigns beginning in 2008 should have been viewed as having comparable potential for contamination with extrinsic foreign particles. Based on your firm's response, there were **(b)(4)** lots of API manufactured in 2008 and **(b)(4)** manufactured in 2009 that had potential to be contaminated with foreign particles. Your investigation found that 22 of the 29 foreign particle types identified were **(b)(4)**. Nonetheless, your firm decided to still use these contaminated lots to produce your **(b)(4)** Capsules **(b)(4)** µg finished product. We are concerned that it was not until July 2012 that your firm began a formal project to implement comprehensive corrections to mitigate the presence of foreign particles in your **(b)(4)** API.

In response to this letter, provide a list of the **(b)(4)** and **(b)(4)** API batches produced after the implementation of the July 2012 CAPA and include whether foreign particles have been observed.

2. Failure to conduct thorough complaint investigations regarding the presence of foreign particles found in your APIs. For example,

    a. In June 2010 your firm received a complaint related to **(b)(4)**, batch **(b)(4)**, manufactured in August 2009, that was contaminated with particles. This batch had been sent to **(b)(4)** located in **(b)(4)** for further manufacturing of **(b)(4)** capsules. Your firm identified the particles as **(b)(4)**. Your investigation did not find the root cause for the foreign particles and concluded that the complaint was "not confirmed." The inspection documented that your firm was aware of the foreign particles present in the **(b)(4)** API since it was discovered in 2009. However, you concluded that the complaint for batch **(b)(4)** was "not confirmed" and closed the investigation.

    b. In September 2011 your firm received a complaint report #5000460 related to 8 small foreign particles described as **(b)(4)** (ranging in size from 0.5 to 3.0mm) in one of the drums of the **(b)(4)** API lot #**(b)(4)**. Your firm's complaint investigation described the foreign particles as **(b)(4)**. Moreover, in December 2011, when complaint investigation #5000460 was opened, your firm received a complaint for **(b)(4)** lot #**(b)(4)**, also related to foreign particle contamination. Your QA unit confirmed that the particles were similar to the particles found in batch **(b)(4)**. Your firm failed to include this lot as part of your investigation. Instead your firm's quality unit closed the complaint for the **(b)(4)** lot **(b)(4)** as "not confirmed," while complaint report #5000460, for **(b)(4)** lot **(b)(4)** was "confirmed" to be related to the manufacturing process. Your determination of "confirmed" or "not confirmed" is inconsistent, as both complaints were related to the presence of foreign particles found in your API, but your final conclusions were different. We are concerned about your inability to prevent the presence of foreign particles in your APIs and the adequacy of actions taken to address the situation.

In response to this letter, please inform this office of the appropriate corrective actions taken by your quality unit to prevent foreign particle contamination in **(b)(4)** and other APIs manufactured by your firm.

FINISHED PRODUCT: CGMP VIOLATIONS

1. Your firm failed to reject drug products that did not meet established standards or specifications and any other relevant quality control criteria (21 CFR 211.165(f)).

Your firm failed to reject multiple batches of **(b)(4)** Capsules **(b)(4)** µg batches that were contaminated with foreign particles. During 2010 and 2012, several lots of **(b)(4)** API batches (lots **(b)(4)**) were contaminated with extrinsic foreign particles found during **(b)(4)**, weighing or by visual inspection and were used for finished drug manufacturing. The size and weight of the particles ranged from approximately 200 microns to approximately 5 mm, from 0.4 micrograms to approximately 9 mg, respectively.

We disagree with your decision to use the **(b)(4)** API because the contaminated batches met the final specifications. Use of appropriate manufacturing, controls, quality standards, and systems for investigations of atypical events (e.g., contamination) are all essential parts of a robust quality system. Additionally, quality cannot be added into a product after it has been manufactured. We are therefore concerned about your decision to use contaminated **(b)(4)** API to manufacture your **(b)(4)** capsules, as this drug is approved for patients diagnosed with **(b)(4)**.

2. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

For example, your firm failed to determine the cause of the OOS for Spiriva HandiHaler lot 908679 that failed the uniformity of delivered dose test specification with a reported value of **(b)(4)**% during the 9-month stability interval. This same lot also failed the uniformity of delivered dose attribute during the 12-month stability interval. It was only after the 12-month OOS result that your firm decided to initiate a product recall for this Spiriva lot. We are concerned about the management decision to allow adulterated product to remain in the market between the 9 and 12 month stability stations.

In response to this letter, please inform this office of the actions your firm will take to prevent recurrence of this situation. Also, provide a retrospective evaluation of all lots currently in the stability program and assess whether an OOS was obtained at any testing interval.

The violations cited in this letter are not intended to be an all-inclusive list 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, 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 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, your failure to correct these violations may result in FDA refusing admission of articles manufactured at Boehringer-Ingelheim Pharma GmbH & Co KG Ingelheim, Germany 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 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 violations, 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 drug product(s) at issue, provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3002806556.

Please send your reply to the following address:

Rafael Arroyo
Compliance Officer
FDA/CDER/OC/OMPQ/DIDQ
10903 New Hampshire Ave.
White Oak Building 51, Room 4237
Silver Spring, MD 20993

Sincerely,
/S/
Michael D. Smedley
Acting Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

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