Inspections, Compliance, Enforcement, and Criminal Investigations

Hameln Pharmaceuticals Gmbh 12/17/12

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: 320-13-06

December 17, 2012

Mr. Christof Kerstein
Hameln Pharmaceuticals GmbH
Langes Feld 13,
D-31789 Hameln, Germany

Dear Mr. Kerstein:

During our June 4th to 14th, 2012 inspection of your pharmaceutical manufacturing facility, Hameln Pharmaceuticals GmbH located at Langes Feld 13, D-31789 Hameln, Germany, investigator(s) from the U.S. 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 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 July 4, 2012, and note that it lacks sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondence dated August 2, 2012, August 31, 2012, and September 28, 2012.

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

1. Your firm failed to ensure that each person engaged in the manufacture, processing, packing, or holding of a drug product has the education, training, and experience, or any combination thereof, to enable that person to perform his or her assigned functions (21 CFR 211.25(a)).

For example, an employee examining **(b)(4)** plates was unable to read and accurately record microbial counts. Additionally, our investigator observed employees functioning in roles supporting your sterile filling operations that were not following the procedures that govern their activities, such as glove change frequency, the handling of dropped objects, personnel monitoring, and sample acquisition. Your responses indicate that the employees observed during the inspection had been trained in their respective job functions and that they have now been re-trained on these procedures, several of which were made more specific. Your response did not provide an explanation for why your system was unable to recognize, identify and

mitigate these performance lapses.

2. Your firm has not established or followed appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile. Such procedures shall include validation of all aseptic and sterilization processes. (21 CFR 211.113(b))

We observed that your smoke study videos were not sufficient to evaluate the quality of your Class A airflow. In your response, you included a written evaluation of the smoke studies. However, the videos you provided as raw data did not provide sufficient evidence to support the conclusions you drew. These studies should show that unidirectional flow is maintained and that particles will be swept away from the critical area. In your response to this letter, provide additional evidence to support your conclusion that sufficient smoke studies were done to evaluate the quality of your Class A airflow or, alternatively, you can repeat the smoke studies.

3. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

There was no justification for the failure to place nonviable probes in locations related to the risk to exposed containers and product. Your placement of non-viable probes in the Class B areas, situated **(b)(4)** from the **(b)(4)**, were also in locations providing information of little value in describing the quality of this adjacent environment that may impact the product.

Your response indicated that one of your restricted access barrier system (RABS) units would be redesigned by March 31, 2013 because it is difficult to use. Please explain what increased risks may have occurred when producing previous batches with this process design, and describe your risk mitigation efforts.

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. For example, it was also noted that your in-house sterility testing method has not been shown to be equivalent to or better than USP <71>. 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.

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 Hameln Pharmaceuticals GmbH in Langes Feld 13, D-31789, Hameln, Germany into the United States under Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3). 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. Please identify your response with FEI # 3002807877.

Please send your reply to the following address: Regina Brown, U.S. Food and Drug Administration, WO Building 51 Room 5212, 10903 New Hampshire Ave, Silver Spring, MD 20993.

Sincerely,
/S/
Steven J. Lynn
Director,
Office of Manufacturing and Product Quality

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U.S. Food and Drug Administration
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