Hikma Farmaceutica, (Portugal) S.A. 10/21/14

Department of Health and Human Services

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

Warning Letter

WL: 320-15-003

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

October 21, 2014

Mr. Said Darwazeh
Chairman and Chief Executive Officer
Hikma Pharmaceuticals Limited
Bayader Wadi Seer
P.O. Box 182400
11118 Amman, Jordan

Dear Mr. Darwazeh:

During our March 20, 2014 through March 28, 2014, inspection of your pharmaceutical manufacturing facility, Hikma Farmaceutica, (Portugal) S.A. located at Estrada do Rio da Mo, N8, 8A E 8B, Fervenca, Terrugen, Portugal, investigators 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 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 conducted a detailed review of your firm’s response dated April 16, 2014, and note that it lacks sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondences dated July 1, 2014, July 22, 2014, September 11, 2014 and October 10, 2014.

Our investigators observed specific violations during the inspection, including, but not limited to, the following:

1. 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 conduct thorough investigations of your environmental monitoring (EM) excursions (i.e., exceeds action levels) found in your Class 100 areas. During the inspection, the review of the available data for the period of January 2012 to December 2013 revealed that your firm identified 23 EM samples that exceeded action levels in the Class 100 aseptic area on Line **(b)(4)** in your building identified as Hikma **(b)(4)**. Our review of the investigations collected during the inspection noted that all investigation reports identified "possible root causes" of the EM excursions as mishandling and/or poor aseptic technique during sampling. In all of these investigations you were unable to determine an actual root cause; yet, you disregarded the EM excursions without justification. In addition, your firm failed to evaluate the potential impact of these EM excursions on the quality of the product manufactured.

Your firm also failed to implement corrections to address possible contributing factors for the isolates recovered during environmental monitoring (EM) in the class 100 areas. Your response states that you will improve the preparation of the EM plates as a corrective action. We disagree with your proposed corrective action since you have no evidence to support your claim that these results may be false positives. Your firm fails to address the possible microbial contamination you may have in your facility.

We note that your firm prepares the media plates used for EM sampling at your site. Prior to using these plates, your firm incubates them for **(b)(4)** and we are concerned that this practice may compromise the media's growth promotion potential. Provide evidence to demonstrate that pre-incubation of the media plates does not adversely impact the ability to promote microbial growth. Absent evidence to support this practice, you lack critical information demonstrating the suitability of the Class 100 production environment to assure product sterility.

We note that the lack of adequate investigations is a repeat violation from your September 2011, June 2007, and March 2004 inspections. In response to this letter provide a comprehensive plan to improve your investigations.

2. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess, and your firm's quality control unit did not review and approve those procedures, including any changes (21 CFR 211.100(a)).

Your firm failed to provide adequate challenge test set vials to qualify your operators and Quality Assurance (QA) staff to perform visual inspection of your drug product. Our investigators identified that 14 of **(b)(4)** vials used to qualify the operators for visual inspection were marked on top of the stopper with a number or a dot that was easily visible to the operator who was holding the vial during qualification. This practice allowed the operator to know in advance which vials were to be rejected.

Your firm's response attributes the use of marked vials to the combining of an old challenge set with a new set without taking into consideration that the vials were previously numbered. Your response is inadequate in that it did not include a product impact assessment for all the batches inspected by operators that were not properly qualified.

In response to this letter describe the actions you have implemented to ensure that the finished parenteral drugs you manufacture are essentially free of particulate matter. Also, provide an assessment of your quality system procedures to detect quality defects in your marketed products.

We note that your firm was previously cited during the September 2011, inspection for failing to detect and evaluate particulates.

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.

Based upon the nature of the CGMP violations identified at your firm during the most recent inspection and previous inspectional findings, it is apparent that Hikma Farmaceutica, (Portugal) S.A.'s attempts to implement global corrective actions have been inadequate. Be advised that corporate management has the responsibility to ensure the quality, safety, and integrity of its drug products. FDA strongly recommends that your corporate management immediately undertake a comprehensive and global assessment of your manufacturing operations, including facility design, procedures, personnel, processes, and systems, including your aseptic processing capabilities, to ensure that drug products conform to FDA requirements.

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 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 Hikma Farmaceutica, (Portugal) S.A. located at Estrada do Rio da Mo, N8, 8A E 8B, Fervenca, Terrugen, Portugal 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 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 products at issue, provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3002807173.

Please send your reply to:

Maan Abduldayem
Compliance Officer
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Manufacturing and Product Quality
Division of International Drug Quality
White Oak, Building 51 room 4212

10903 New Hampshire Ave.
Silver Spring, MD 20993

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

cc:
Mr. Riad Ali Mechlaoui
EU Vice President and Global Head of Injectables
Hikma Farmaceutica, (Portugal) S.A.
Estrada do Rio da Mo, N8, 8A E 8B
Fervenca, Terrugen
Portugal