Ebewe Pharma Ges MBH Nfg KG 5/28/13

Department of Health and Human Services

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

Warning Letter

WL: #320-13-19

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

May 28, 2013

Mr. Joseph Jimenez
CEO Novartis
Novartis International AG
Forum 1, Novartis Campus
CH-4056 Basel / Switzerland

Dear Mr. Jimenez:

During our October 15-23, 2012, inspection of your pharmaceutical manufacturing facility, Ebewe Pharma Ges. m.b.H Nfg. KG located at Mondseestrasse 11, A-4866 Unterach am Attersee, Austria, 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. In addition, the **(b)(4)** Injection **(b)(4)** mg/mL and **(b)(4)** Injection **(b)(4)** mg/mL that you distributed without the required FDA marketing application is an unapproved new drug under section 505(a) of the Act (21 U.S.C. §355(a)).

We acknowledge receipt of your firm's correspondence dated November 14, 2012.

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

1. Your firm failed to obtain FDA's approval of changes in the quality controls established in an approved application prior to distributing the product made using the changes (21 C.F.R. §314.70(b)).

For example, your firm manufactured and distributed **(b)(4)** lots of finished parenteral drugs (**(b)(4)** lots of **(b)(4)** Injection **(b)(4)**mg/mL and **(b)(4)** lots of **(b)(4)** Injection **(b)(4)** mg/mL) to the U.S. market using unapproved procedures for visual inspection prior to obtaining approval of a supplement regarding these changes.

FDA informed your firm several times, in writing and orally, not to distribute the implicated product until you received approvals of the supplements. FDA further informed your firm in writing on March 14, 2012, that these supplements were not approvable. Although your firm ceased using the unapproved method, you failed to provide a plan to address the products distributed in the U.S. market that used the method.

In your response to this letter, confirm the distribution information of all the **(b)(4)** and **(b)(4)** lots manufactured by your firm using unapproved methods. Provide your risk assessment for allowing these lots to remain on the market, taking into account all relevant information including FDA's list of reasons for not approving the supplements provided to you on March 14, 2012. In addition, include a complete list of products you manufacture and a commitment to audit your current production procedures against the standards established in approved applications (including approved supplements). Also, provide an action plan to appropriately address each discrepancy identified by the audit. Finally, in your response to this letter, describe the specific corrective actions your firm is implementing to ensure adherence to application commitments in the future, as well as proper evaluation and handling of proposed changes to them. Please detail how you will ensure that Agency approval of a supplemental application is obtained prior to implementation of changes, and how you will ensure that such changes are effected only after providing the Agency appropriate notice.

2. Your firm failed to establish a scientifically sound and appropriate test procedure to determine conformance of the finished drug product to an established specification (21 CFR 211.160(b)).

The procedures established to perform the visual inspection of critical defects, such as particulate matter in finished parenteral drug vials, are inadequate in that operators following these procedures have repeatedly failed to detect visible particles.

At least on 10 occasions, your firm's inspection of finished product vials failed to detect **(b)(4)**, **(b)(4)**, and residues of unknown composition (e.g., **(b)(4)** diluent batches **(b)(4)**, and **(b)(4)**, **(b)(4)** batch **(b)(4)**/Solvent batch **(b)(4)**, and **(b)(4)** batch **(b)(4)**). Although we recognize that in some instances your firm rejected batches with these defects, we are concerned that you did not detect visible particles until after release of other affected lots. Because your lot inspection failed to detect visible particle matter in numerous instances, we are concerned that your inspection program is not robust enough to serve its intended purpose.

In your response to this letter, describe the actions you have taken to assure that the finished parenteral drugs you manufacture are essentially free of particle matter. Describe your revised inspection program and your enhanced AQL program. Indicate impact of the particle defects on product produced for the U.S. market.

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 Staff 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 Staff 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 Ebewe Pharma Ges. m.b.H Nfg. KG located at Mondseestrasse 11, A4866 Unterach am Attersee, Austria 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).

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.

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 # 3002829723.

Please send your reply to the following address:

Milva Meléndez
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, RM 4316
10903 New Hampshire Ave
Silver Spring, MD 20993

Sincerely,
/S/
Michael D. Smedley
Acting Director
Office of Manufacturing and Product Quality

cc: Mr. Ulrich H. Valley
Head of Unterach Site
Ebewe Pharma Ges.m.b.H. Nfg. KG
Mondseestrasse 11
A-4866 Unterach am Attersee / Austria

Close Out Letter

- **Ebewe Pharma Ges MBH Nfg KG - Close Out Letter 9/14/15 (/ICECI/EnforcementActions/WarningLetters/2015/ucm463620.htm)**

More in 2013 (/ICECI/EnforcementActions/WarningLetters/2013/default.htm)