WARNING LETTER

Europharma Concepts Limited

MARCS-CMS 544738 — MAY 16, 2018

Recipient:

Mr. Michael Gilmore

Europharma Concepts Limited

Kilbeggan Road, Clara Tullamore
County Offaly
Ireland

Issuing Office:

Center for Drug Evaluation and Research

United States

U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-18-52

May 16, 2018

Mr. Michael Gilmore
General Manager
Europharma Concepts Limited
Kilbeggan Road, Clara Tullamore
County Offaly
Ireland

Dear Mr. Michael Gilmore:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Europharma Concepts Limited at Kilbeggan Road, Clara Tullamore, County Offaly, from October 31 to November 3, 2017.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug product is adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your November 24, 2017, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific violations including, but not limited to, the following.

1. Your firm failed to test samples of each component for conformity with all appropriate written specifications for identity, purity, strength, and quality (21 CFR 211.84(d)(1) and (2)).

Your firm uses glycerin as an ingredient in your over-the-counter (OTC) **(b)(4)** Gel, a drug product intended for **(b)(4)** use in **(b)(4)**. Your firm failed to analyze lots of glycerin raw material from your supplier for the presence of diethylene glycol (DEG) and ethylene glycol (EG) prior to releasing it for use in drug product manufacturing. DEG contamination in glycerin has resulted in various lethal poisoning incidents in humans worldwide.

Furthermore, your firm failed to test your incoming active pharmaceutical ingredient, **(b)(4)**, and other components you use in manufacturing **(b)(4)** Gel OTC drug product to ensure that each component met all specifications, including testing for identity prior to release for use in manufacturing.

In your response, you state that you contacted your suppliers of raw materials that do not appear in the United States Pharmacopeia-National Formulary compendium, and that you are collecting and evaluating test methods for these materials.

Your response is inadequate because as a manufacturer you are responsible for performing a specific identity test for all component lots prior to release for use in drug product manufacturing. You also failed to describe your interim actions to ensure that all raw material lots meet their specifications before use in manufacturing. For example, with respect to your glycerin-containing products, you have not addressed whether DEG or EG is present in any of the glycerin lots used to manufacture drug products intended for administration to **(b)(4)**.

In response to this letter:

- Provide written procedures for how you will qualify your suppliers, both initially and on an ongoing basis. Describe whether you intend to test each lot of incoming components for all attributes. Alternatively, if you intend to rely on the supplier's certificate of analysis, provide specifics on how you will verify each suppliers' test results at regular intervals and include a commitment to test every incoming component lot for identity, at minimum.
- Provide a detailed risk assessment for drug products that contain glycerin and are within expiry in the U.S. market. Test retain samples of all lots for DEG and EG. If you find that you released any batch for which results are out-of-specification, indicate the corrective actions you will take, such as customer notifications and product recalls.
- Provide a comprehensive, independent review of your laboratory practices, methods, equipment, and analyst competencies. Based on this review, provide a detailed corrective action and preventative action plan to fully remediate your laboratory system.

See FDA's guidance document, *Testing of Glycerin for Diethylene Glycol*, to help you meet the CGMP requirements when manufacturing drugs containing glycerin, at https://www.fda.gov/downloads/Drugs/Guidances/ucm070347.pdf (/media/71029/download).

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)).

You failed to perform process validation for your **(b)(4)** Gel OTC drug product. You did not demonstrate that your manufacturing process is reproducible and controlled to consistently yield drugs of uniform character and quality.

We acknowledge that you have ceased manufacturing your **(b)(4)** Gel **(b)(4)**% OTC drug product and in a subsequent response, you stated that your **(b)(4)** for manufacturing **(b)(4)** Gel **(b)(4)**% OTC drug product. You also stated, "It is not viable either contractually or commercially to incorporate it into extensive validation activities."

Your response is unacceptable because you have not addressed product currently in the U.S. market that you manufactured using a process that was not validated. If you manufacture drug products for the U.S. market, you must validate your manufacturing process to ensure that it is reliable and reproducible prior to marketing any drug product.

Your firm lacks a process validation program. Process validation evaluates the soundness of design and state of control of a process throughout its lifecycle. Each significant stage of a manufacturing process must be designed to assure the quality of raw material inputs, in-process materials and finished drugs. Process qualification studies provide a determination whether an initial state of control has been established. Successful process qualification studies are necessary prior to commercial distribution. Thereafter, ongoing vigilant oversight of

process performance and product quality is necessary to ensure you maintain a stable manufacturing operation throughout the product lifecycle.

See FDA's guidance document, *Process Validation: General Principles and Practices*, for general principles and approaches that FDA considers appropriate elements of process validation, at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf (/media/71021/download).

In response to this letter, provide improved procedures regarding validation/verification requirements, updated analytical methods, and your validation plans if you intend to resume manufacturing products for the U.S. market.

Responsibilities as a contractor

Drugs must be manufactured in conformance with CGMP. FDA is aware that many drug manufacturers use independent contractors, such as production facilities, testing laboratories, packagers, and labelers. FDA regards contractors as extensions of the manufacturer.

You and your customer, **(b)(4)**., have a quality agreement regarding the manufacture of **(b)(4)** Gel OTC drug product. You are responsible for the quality of drugs you produce as a contract facility, regardless of agreements in place with product owners. You are required to ensure that drugs are made in accordance with section 501(a)(2)(B) of the FD&C Act for safety, identity, strength, quality, and purity. See FDA's guidance document, *Contract Manufacturing Arrangements for Drugs: Quality Agreements*, at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM353925.pdf (/media/86193/download).

CGMP consultant recommended

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements. The third party should comprehensively audit each system in your operation for CGMP compliance. Your corrective and preventive actions should be evaluated by the third party to help ensure systemic remediation before you pursue resolution of your firm's compliance status.

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

Conclusion

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations.

FDA placed your firm on Import Alert 66-40 on February 22, 2018.

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations may also result in FDA continuing to refuse admission of articles manufactured at Europharma Concepts Limited, Kilbeggan Road, Clara Tullamore, County Offaly, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles may be subject to refusal of admission, 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 FD&C Act, 21 U.S.C. 351(a)(2)(B).

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov) or mail your reply to:

Carla Norris
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3011798296.

Sincerely,
/S/
Francis Godwin
Acting Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

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