Goran Pharma Pvt Ltd 4/24/18

U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-18-48

April 24, 2018

Mr. Hemant D. Dholakia
Managing Director
Goran Pharma Private Limited
GDIC-I, Bhavnagar Road
Sihor, Gujarat 364240
India

Dear Mr. Dholakia:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Goran Pharma Private Limited at GDIC-I, Bhavnagar Road, Sihor, Gujarat, from November 13 to 15, 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 products are 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 December 15, 2017, response in detail and acknowledge receipt of your subsequent correspondence.

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

1. Your firm failed to ensure the identity of components, including your active ingredients and excipients from various suppliers (21 CFR 211.84(d)(1) and (2)).

You failed to test incoming components you use in manufacturing drug products to determine their conformance to identity, purity, strength, and other appropriate specifications. Your firm released components for use in drug product manufacturing based on certificates of analysis (COA) from your supplier without establishing the reliability of the suppliers' analyses through appropriate validation. For example, your firm did not test each lot of glycerin used as a component of your drugs to determine whether diethylene glycol (DEG) or ethylene glycol (EG) was present. Because you did not test each glycerin lot using the USP identification test that detects these hazardous impurities, you failed to assure the acceptability of lots used in drug product manufacture. DEG contamination in pharmaceuticals has resulted in various lethal poisoning incidents in humans worldwide.

Your response indicated that you will compare your laboratory results with the supplier's COA to confirm the reliability of testing for all lots, and you provided a revised standard operating procedure (SOP) *Purchasing, Supplier Approval, Monitoring, and Risk Analysis* (SOP No. GPPL/PUR/01). The revised SOP, provided with your response as Annexure 30, also discusses adding suppliers to an "approved vendor list."

Your response is inadequate because it is not clear whether you will indefinitely test each incoming component lot for all attributes to verify the accuracy of your suppliers' COA, or you will instead qualify your suppliers' test results through an initial round of testing as well as ongoing testing at appropriate intervals. Additionally, your response did not address whether your firm conducted retrospective DEG and EG testing for products distributed to the United States.

In response to this letter, provide the following:

- a detailed description of how you will ensure that components (e.g., ingredients) used in the manufacture of your drug products will be withheld from use until the lot has been tested in accordance with the current United States Pharmacopoeia (USP) and released for use by the quality unit;
- an improved procedure that describes how you qualify your suppliers' COA both initially and on an ongoing basis. Explain whether you intend to test each lot of incoming components for all attributes instead of relying on the suppliers' COA. Alternatively, if you intend to rely on the supplier's COA, provide specifics on how you will verify each supplier's test results at regular intervals and include a commitment to test at minimum every incoming component lot for USP identity requirements.
- a detailed risk assessment for drug products that contain glycerin and are within expiry in the U.S. market. As part of your risk assessment, immediately test retained samples of all lots for DEG and EG, and take appropriate market action if the testing yields any aberrant results.
- a comprehensive, independent review of your laboratory practices, methods, equipment, and analyst competencies. Based on this review, provide a detailed corrective action and preventive action (CAPA) plan to remediate your laboratory systems.

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 (https://www.fda.gov/downloads/Drugs/.../Guidances/ucm070347.pdf)**.

2. Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products (21 CFR 211.22(a)).

Your quality unit released batches without reviewing all production and control records. You shipped the **(b)(4)** batch **(b)(4)** prior to completion of microbiological testing. Your SOP *Issue Batch No., Issue, Entry, Review and Control of BMR and Batch Release* (SOP GPPL/QC/04) allows this practice.

Your response is inadequate because your revised SOP, supplied with your response as Annexure 31, states that in cases of "emergency" you will transfer the product to the shipping agent's warehouse with a "not for sales" [*sic*] COA. This indicates that finished product may still be distributed prior to completion of testing and review by your quality unit. Your SOP continues to state that if a failing result is obtained you will conduct a "recall/withdrawal" from the shipping agent.

In response to this letter, submit updated procedures and corrective actions to ensure that your quality unit will review complete records prior to making a finished product batch disposition decision. Additionally, provide a CAPA that establishes an adequate quality unit with the appropriate authority and sufficient resources to carry out its responsibilities and consistently ensure drug quality.

3. Your firm failed to use equipment in the manufacture, processing, packing, or holding of drug products that is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance (21 CFR 211.63).

Your **(b)(4)** system was not appropriately designed. The system, which you indicated was "sterilized" **(b)(4)**, contained **(b)(4)** piping with dead legs. This inappropriate system design fosters the development of biofilms. Moreover, due to the deficiencies noted in laboratory controls during the inspection, such as inappropriate storage of media, lack of growth promotion testing, and lack of positive controls, it is not certain you would be able to reliably detect bioburden or microbial limits failures.

In your response you stated you have procured an improved **(b)(4)** system. Your response is inadequate because it lacks detail on how you will validate the new **(b)(4)** system. You stated that you will "sterilize" the new **(b)(4)** system **(b)(4)** with **(b)(4)** for **(b)(4)**, but you did not provide scientific rationale for the proposed frequency, **(b)(4)**, or duration. Lastly, your response did not include a risk assessment for products within your control or that have been distributed to the United States that were manufactured using the previous **(b)(4)** system.

In response to this letter provide the following:

- a detailed plan for validation of the new **(b)(4)** system
- procedures for routine monitoring of the **(b)(4)** system as well as system control and maintenance
- scientific justification for the frequency, **(b)(4)**, and duration that you will use to sanitize the **(b)(4)** system
- a risk assessment for products manufactured prior to installation and validation of the new **(b)(4)** system
- your rationale for relying on past data to characterize the **(b)(4)** system's state of control, given the microbiology laboratory deficiencies noted during the inspection.

4. Your firm failed to provide equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature when appropriate for the manufacture, processing, packing, or holding of a drug product (21 CFR 211.46(b)).

You lacked an air handling system as well as control and monitoring of temperature and humidity in the manufacturing (e.g. filling, packaging) and warehouse areas. You confirmed that your drug products may be exposed to temperatures over 30°C (86°F) and that temperatures in your facility can reach 50°C (122°F) during hot weather months.

It is unacceptable to manufacture drug products without an air handling system that has control over temperature, humidity, and air cleanliness. Your lack of air handling systems and control has the potential to adversely affect the quality of your raw materials, in-process materials, and finished products.

In response to this letter, provide the following:

- a detailed action plan for ensuring adequate control and monitoring of temperature, humidity, and air cleanliness in your facility
- a comprehensive, independent assessment of your facilities and equipment. This assessment should include a full evaluation of the suitability of the design, control, and maintenance of your equipment and facilities. Based on this review, provide a detailed CAPA plan.

Quality Unit Authority
Significant findings in this letter indicate that your quality unit is not fully exercising its authority and/or responsibilities. Your firm must provide the quality unit with the appropriate authority, sufficient resources and staff to carry out its responsibilities and consistently ensure drug quality.

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 consultant should comprehensively audit your entire operation for CGMP compliance, with special emphasis on the materials, laboratory, facility, and production systems, as well as your overall quality assurance program. Your CAPA should be evaluated by the third party to help ensure thorough and 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 March 5, 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 Goran Pharma Private Limited, GDIC-I Bhavnagar Road, Sihor, Gujarat, 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:

LCDR Catherine Gould, Pharm.D.
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 3009336980.

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

More in Warning Letters (/ICECI/EnforcementActions/WarningLetters/default.htm)