Labocont Industrial SRL 3/9/18

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-18-39

March 9, 2018

Mr. Leodoro A. Contreras
Owner
Labocont Industrial SRL
Entrada Zona Franca, La Caleta Autopista Las Américas
Km 19 Santo Domingo, 11606
Dominican Republic

Dear Mr. Contreras:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Labocont Industrial SRL at Entrada Zona Franca, La Caleta Autopista Las Américas, Km 19 Santo Domingo, from June 5 to 9, 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 July 13, 2017, response in detail and acknowledge receipt of your subsequent correspondence. Your response failed to commit to specific and comprehensive actions to address the violations observed during the inspection.

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

1. Your firm failed to perform operations within specifically defined areas of adequate size and to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups (21 CFR 211.42(c)).

Your firm manufactures **(b)(4)** and non-**(b)(4)** drug products in the same facility. For example, **(b)(4)** and **(b)(4)** are manufactured along with over-the-counter (OTC) **(b)(4)** non-**(b)(4)** drug products. Your firm does not completely and comprehensively separate **(b)(4)** production facilities, which presents an unacceptable risk of **(b)(4)**contamination in other drug products manufactured at your facility.

(b)(4)

In response to this letter:

- Summarize all in-date batches of drug products produced at your facility and distributed in the U.S. market, and perform a thorough risk assessment of the impact of conducting **(b)(4)** and non-**(b)(4)** manufacturing operations within the same facility.
- Outline your proposed market action plan, including customer notifications and recalls, to address all products in the U.S. supply chain at risk for potential **(b)(4)** contamination.
- Provide your plan to completely and comprehensively separate your facility for the manufacture of **(b)(4)** drugs. Commit to one of the following two options for the facility you have used to manufacture **(b)(4)**.
    - *Dedicate the facility to* **(b)(4)** *production only.* We strongly urge you to dedicate the facility to **(b)(4)** only production. It is unacceptable to produce any other products in the same physical facility. If you intend to choose this option, provide your timeline for implementation. Also, be advised that it is inappropriate for different classes of **(b)(4)** to be manufactured in the same facility. Significantly, our inspection found that you are currently producing **(b)(4)** and non-**(b)(4)** for other markets within the same facility, rather than in separate dedicated facilities.
    - *Fully decontaminate the facility*. It is profoundly difficult to completely decontaminate a facility of **(b)(4)** residues. If you intend to attempt decontamination so that your facility can resume solely non-**(b)(4)** production, provide a comprehensive decontamination plan for the facility. Also, provide highly-sensitive methods to detect any **(b)(4)** and **(b)(4)** residues throughout the facility, and address all potential sources of cross-contamination of **(b)(4)** into non-**(b)(4)** drugs. You should not introduce any drug products into the U.S. supply chain until FDA determines that your proposed decontamination plan, methods, and procedures are adequate, thorough, comprehensively implemented, and verified via an FDA inspection.

2. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

Your firm does not ensure that complete data from assay testing of your finished drug products and active pharmaceutical ingredients (API) are maintained and reviewed by your quality unit. For example, our investigator observed that an analyst failed to document absorbance data generated during assay analysis, and only reported calculated results.

Because you do not document and maintain complete data from your analyses, it is not possible to evaluate whether the method was followed and data is valid, or to substantively investigate sources of deviations and variation in your laboratory. It is essential that all data generated during analysis is maintained and reviewed to determine whether laboratory procedures are followed, and raw materials and drug products conform to established specifications.

In response to this letter:

- Provide a comprehensive investigation into the inadequacies in data records and reporting for all products manufactured for the U.S. market and within expiry. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. In addition, describe all parts of your facility's operations in which CGMP information is not recorded and maintained. Include a corrective action and preventive action (CAPA) plan to remediate data recording and retention practices throughout your operation.
- Provide a risk assessment summarizing the affect of incomplete data on assessing laboratory control and product quality.
- Provide a detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all the data you generate, including analytical and manufacturing data. This should include procedures that detail your documentation, data evaluation, review, retention, and quality oversight practices. Outline how you will assess your corrective actions for effectiveness.

3. Your firm failed to establish and document the accuracy, sensitivity, specificity, and reproducibility of its test methods (21 CFR 211.165(e)).

The analytical methods that you used to determine assay of your API and finished drug products are not validated and lack specificity. In addition, you did not calibrate or verify instrumentation used to perform laboratory tests. There is no assurance that your test methods and instrumentation generate accurate and reliable data.

In response to this letter:

- Provide an independent assessment of the suitability of your firm's test methods and adequacy of methods validation (or verification, for compendial methods) performed for all drug products for U.S. supply and raw materials.
- Provide your plan of action to complete validation (or verification, for compendial methods) for all analytical methods used in association with products that are shipped to the U.S.
- Provide a comprehensive independent review of your entire laboratory system, and a CAPA plan that ensures full remediation of the laboratory operation. For example, the review of your laboratory system should include, but not be limited to, the suitability of all laboratory equipment, a fully remediated calibration program, staff competencies, supervisory oversight, data systems, and other elements of laboratory control.

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. We also recommend that your qualified third party consultant perform comprehensive audits of your facility, to include all laboratories and manufacturing operations, with special emphasis on proper facility design, laboratory operations, records integrity, process control and management oversight. Your corrective and preventative actions should be fully 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 for 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 8, 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 refusing admission of articles manufactured at Labocont Industrial SRL at Entrada Zona Franca, La Caleta Autopista Las Américas, Km 19 Santo Domingo, 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:

Ms. Christina Alemu-Cruickshank
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 3010166941.

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

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