Les Produits Chimiques B.G.R., Inc. 7/24/18

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter WL 320-18-64

July 24, 2018

Mr. Sylvain Chevrier
President
Les Produits Chimiques B.G.R., Inc.
600 Avenue Delmar
Pointe-Claire
H9R A48, Quebec, Canada

Dear Mr. Chevrier:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Les Produits Chimiques B.G.R., Inc. at 600 Avenue Delmar, Pointe-Claire, Quebec, from September 25 to 27, 2017.

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API 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 October 17, 2017, response in detail.

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

1. Failure to perform laboratory testing of API to ensure conformance to specifications and to accurately report results on certificates of analysis (COA).

Your firm distributed multiple lots of **(b)(4)** powder USP API without completing required release testing for identity. Your COA reported that these drugs met all required specifications. We reviewed your firm's COA and laboratory notebooks for **(b)(4)** powder

USP lot #**(b)(4)**, as well as for multiple lots of this product dating back to at least 2015. The laboratory notebooks lacked the analytical data to support the information on your COA. Your firm confirmed to our investigator that, although your COA states that the identity tests "Passed," you did not perform the tests. Although you never performed the required testing, you distributed these API lots to the U.S. market with false information on the COA.

In your response, you provided the identity test results for lots produced since 2015; you conducted these retrospective analyses only after our inspection identified that you had never performed the tests in the first place. Your response is inadequate. While you tested lots identified during our inspection that were manufactured since 2015, you did not test all distributed lots within expiry. In addition, you did not conduct a thorough review of all release records to determine whether the test results for other drug quality attributes were falsely reported.

Customers and regulators rely on certificates of analysis for critical information about the quality and source of their ingredients. Unreliable information on a COA compromises supply-chain accountability and quality assurance, and may put consumers at risk.

In response to this letter, provide the following.

- A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Include a detailed description of the scope and root causes of your data integrity lapses.
- A current risk assessment of the potential effects of the data integrity deviations on the quality of your API. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity.
- A management strategy for your firm that includes the details of your global corrective action and preventive action plan. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm, including laboratory data and manufacturing records.

2. Failure of your quality unit to exercise its responsibility to ensure the API manufactured at your facility are in compliance with CGMP.

Your quality unit failed to perform a number of critical functions to ensure that the **(b)(4)** powder USP API was manufactured according to CGMP. For example, your quality unit failed to ensure that the records it reviewed included complete data derived from all tests conducted to ensure compliance with established specifications and standards prior to the distribution of an API batch. Your quality unit did not document details such as sample weight and preparation for tests such as **(b)(4)** content, **(b)(4)**, **(b)(4)** or **(b)(4)** and **(b)(4)** content.

Your quality unit also failed to ensure that samples intended for stability studies are stored with controlled temperature and humidity. Your firm kept retain and stability samples of **(b)(4)** USP in a cabinet in the quality control laboratory without monitoring temperature and relative humidity.

In addition, your quality unit did not ensure the cleanliness of buildings and facilities used to manufacture API. You lacked sufficient controls to prevent the presence of pests in your packaging material storage area. At least twice, our inspector observed insects and spider webs in and on plastic-wrapped stacked containers used for packaging API.

Your quality unit also did not ensure that your cleaning validation records are accurate and contain appropriate documentation. For example, you did not document rinse times in your study to validate cleaning of the **(b)(4)** you use to manufacture API.

In your response, you stated that you would:

- update your documentation procedure to clarify the information that is to be recorded in laboratory notebooks;
- purchase a stability chamber and improve your stability program;
- clean and transfer packaging materials to a location in the warehouse where you prevent entry of pests, and train personnel on packaging material inspection requirements;
- repeat your cleaning validation with documented rinse times, and update corresponding cleaning procedures and checklists.

Your response did not provide sufficient detail or evidence that your proposed corrective actions and preventive actions (CAPA) will bring your operations into compliance with CGMP.

In response to this letter, provide the CAPA plans and procedures you have implemented to ensure that the roles and responsibilities of the quality unit are clearly defined and established. This should include but not be limited to assuring your quality assurance unit has the appropriate authority and resources needed to carry out its responsibilities.

Also provide:

- a revised documentation procedure that specifies the detailed information that must be recorded in laboratory notebooks;
- evidence to demonstrate that you have purchased and qualified a stability chamber, as well as your updated stability protocol;
- your procedures for appropriate storage and inspection of raw materials;
- the report that summarizes your new cleaning validation studies; and
- your revised cleaning procedures and checklists.

Consultant Requested

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 recommend that the qualified third party perform a comprehensive audit of your entire operation for CGMP compliance, including data integrity, and evaluate the completion and effectiveness of any corrective actions and preventive actions.

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.

Additional API CGMP Guidance

FDA considers the expectations outlined in ICH Q7 in determining whether API are manufactured in conformance with CGMP. See FDA's guidance document, *Q7 Good*

Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, for guidance regarding CGMP for the manufacture of API, at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497.pdf

Conclusion

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

Until you correct all deviations 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 deviations may also result in FDA refusing admission of articles manufactured at Les Produits Chimiques B.G.R., Inc. 600 Avenue Delmar, Pointe-Claire, Quebec, 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 deviations 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 or mail your reply to:

Hien K. Lieu
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 3000287309.

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