Lernapharm (Loris) Inc. 9/4/18

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-18-73

September 04, 2018

Mr. Razmik Margoosian
President
Lernapharm (Loris) Inc.
2323 Halpern St.
Saint-Laurent, Montreal
Quebec, Canada H4S 1S3

Dear Mr. Razmik Margoosian:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Lernapharm (Loris) Inc. at 2323 Halpern St., Saint-Laurent, Montreal, from December 4 to 12, 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 22, 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 establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

You failed to adequately validate your drug manufacturing process for your **(b)(4)** drug products that you claim achieves "**(b)(4)** sterilization." These products are labeled as sterile and are intended for significant indications, including "**(b)(4)**."

For example, you reprocessed multiple batches of **(b)(4)** drug products, which purport to be sterile, that did not meet process parameters or quality attributes. In one instance, you reprocessed **(b)(4)** Lot **(b)(4)** after five biological indicator (BI) strips were found with microbial growth.

Your **(b)(4)** process relies on the exposure of your **(b)(4)** drug products to **(b)(4)** of approximately **(b)(4)** for your **(b)(4)**, and per your process summary report, a minimum of **(b)(4)** within the product bins placed in various other locations around the room.

You failed to test the sterility of finished product batches produced by this process, and instead relied on use of a biological indicator organism **(b)(4)**.

Your response states that you do not perform finished product sterility testing because you maintain written records and validation procedures for your parametric release "sterilization program."

Your response is inadequate. Your firm lacks an adequate sterilization method. You have not demonstrated an ongoing state of control and your products, which purport to be sterile, are produced using manufacturing methods that are inappropriate to support this claim.

In addition, parametric release is only appropriate for robust sterilization methods (e.g., steam sterilization). The robust sterilization method must also be augmented by a strong sterility assurance program, an extensive ongoing characterization of batch process control, and a vigilant quality system. See FDA's Compliance Policy Guide (CPG) **(b)(4)** entitled, **(b)(4).**

In response to this letter, describe corrections to your manufacturing operation that will establish a high level of sterility assurance. If you intend to implement a terminal sterilization process, provide a robust sterilization method and rigorous validation protocol that assures the new method achieves a sterility assurance level of 10^{-6} or more (e.g., provide **(b)(4)** and **(b)(4)** data for any **(b)(4)** sterilization method), and uses an appropriate resistant biological indicator that represents the worst-case resistance of microbes that could be found in your environment and product. Regarding the latter, include **(b)(4)** determinations for each biological indicator lot to demonstrate its resistance to the specific sterilization method proposed for use by your firm.

If you plan to continue use of your current **(b)(4)** step at the conclusion of processing, describe the facility and process improvements that will ensure that units subjected to that step are first produced by aseptic processing.

Also include the microbiological testing procedures that you will be using in your process validation studies for in-process and finished product testing. Regarding **(b)(4)** sterility testing, provide your test method, validation protocol, and validation report.

In addition, provide sterility testing results for all batches of your purportedly sterile **(b)(4)** batches that have been released and are within expiry. If such testing reveals substandard quality drug products, provide your corrective actions, including notifying customers and product recalls.

2. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

You failed to conduct thorough investigations into customer complaints for your **(b)(4)** drug products which purport to be sterile. You did not evaluate all potential causes for customer complaints or extend the investigation to other potentially affected batches and other products.

For example, you received complaints AR-17-49 (October 23, 2017) and AR-17-50 (October 25, 2017) due to a significant number of leaking **(b)(4)** of **(b)(4)**. Your investigation found that the **(b)(4)** seals leaked due to pinholes in the package caused by debris that had accumulated on the sealing **(b)(4)** of the packaging machine. However, your investigation did not include your assessment of the following:

- other potential contributors to the pinhole problem, such as packaging material integrity prior to production;
- risks that the leaking packages pose to patients and product quality, including lack of sterility;
- effectiveness of your corrective actions and preventive actions (CAPA); and
- full evaluation of scope and magnitude to determine impact of the manufacturing problems on other batches of **(b)(4)** and additional products you manufacture.

In addition, your investigations into non-integrity complaints for various products routinely lacked examination of retain samples.

Your response acknowledges deficiencies in your investigation systems. However, your risk assessment addressing loss of product sterility due to packaging "deterioration" was inadequate. The assessment indicates that the residual risk rating is "low" for consumer exposure to the defective products. Your risk assessment appears to underestimate the hazards of microbial contamination of products with **(b)(4)** or similar significant indications. Further, you determined that 18 other batches could have been affected by debris on the sealing **(b)(4)**, but you provided no information regarding your investigations into the additional batches.

In response to this letter, provide:

- Your comprehensive investigations into the additional 18 batches potentially affected by debris on the sealing **(b)(4)**, including your CAPA and a plan to ensure its effectiveness. If these investigations reveal any substandard quality drug products, provide actions that you will take such as notifying customers and product recalls.
- An update on your root-cause evaluations and related CAPA for all complaints you received relating to non-integral containers (e.g, leaking containers, dried contents), with special emphasis on further mitigation of human factors associated with the manufacturing process, in-process checks, and final inspection.
- An improved process for risk assessment.
- Your updated assessment of patient hazards associated with loss of package integrity.
- A comprehensive, independent assessment of your overall system for investigations of deviations, atypical events, complaints, out-of-specification results, and failures. Your CAPA should include but not be limited to improvements in investigation competencies, root-cause analysis, remediation, written procedures, and quality unit oversight. Also, include your process for evaluating CAPA effectiveness.

3. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of such stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)).

Your firm lacks stability data to support the **(b)(4)**-month expiration date for your **(b)(4)** drug products, including **(b)(4)**. For example, your stability studies did not include testing for sterility or container-closure integrity at least at expiry for your stability batches. You received multiple customer complaints of leaking **(b)(4)** containers and determined the root cause to be your sealing process.

It is essential for products to maintain container-closure integrity throughout the labeled expiration period to assure their microbiological and chemical quality.

In your response, you provided a summary of test results at 27 months for your oldest available retains of **(b)(4)**. These test results included attributes such as sterility, package integrity, assay, and pH. You state that combining this data with six months of your already acquired accelerated stability data allows you to extrapolate your real-time stability data to 39 months. Your response is inadequate. You failed to provide data demonstrating your **(b)(4)** products maintain sterility and the integrity of their container-closure system throughout their entire **(b)(4)**-month labeled shelf life.

In response to this letter, provide:

- a full summary of stability data results for all batches tested, with each time interval, attributes tested, the testing methods used, and the written stability protocol that was followed. Include testing of all microbiological and chemical attributes, and any updated test data to determine whether the integrity of your container-closure systems (and products are sterile, as applicable) is maintained throughout the entire shelf life.
- a comprehensive assessment and CAPA to ensure the adequacy of your stability program. Your CAPA should include, but should not be limited to a remediated standard operating procedure (SOP) describing your stability program; stability-indicating methods; stability studies to support each drug product in its container-closure system before distribution is permitted; an ongoing program in which representative batches of each product are added each year to the program to determine if the shelf-life claim remains valid; and specific attributes to be tested at each station.

4. Your firm failed to use appropriate air filtration systems for production areas (21 CFR 211.46(c)).

Your firm manufactures **(b)(4)** products, which purport to be sterile, in areas of insufficient control and air classification. These conditions are inadequate to protect the drug and its container-closure systems during drug production.

Sterile products should be produced in cleanrooms that are designed and controlled to meet appropriate cleanliness standards.

In response to this letter provide the following:

- a protocol to review your **(b)(4)** filling and sealing zone, and support room environments, to determine whether they meet appropriate air classification standards, and any associated plans for facility upgrades.
- a comprehensive identification of all contamination hazards in your manufacturing operations and an independent risk assessment that includes, among other things, your manufacturing processes, equipment, and facilities to ensure their suitability for sterile production; and
- a detailed CAPA plan that describes all actions to be taken relating to facilities, equipment, manufacturing methods, controls, people, and raw materials to assure sterility.

5. Your firm failed to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups (21 CFR 211.42(c)).

You failed to establish a program to evaluate the microbiological quality of the environment in which you manufacture **(b)(4)**, which purports to be sterile. For example, environmental monitoring is performed very infrequently (i.e., **(b)(4)**). It does not cover all production **(b)(4)**. It also employs limited passive microbiological testing while lacking personnel monitoring and surface monitoring of your firm's equipment and facilities. The level of monitoring is insufficient to evaluate whether a manufacturing environment is operating in a state of control. You have minimal information on the identity of microorganisms in your environment.

An adequate environmental monitoring program provides timely and sufficient data to assess ongoing control of the environment and assists in assuring low pre-sterilization bioburden. The program should set appropriate alert and action limits, as well as detect adverse environmental conditions and trigger prompt corrective actions that prevent contamination.

In response to this letter, provide your environmental monitoring procedures. These procedures should include appropriate:

- frequency, location, and duration of sampling; sample size; and specific sampling equipment and techniques;
- action and alert limits for each location, and a description of its function and ISO classification;
- instructions regarding investigations of out-of-limit (OOL) environmental monitoring results; and
- identification of microorganisms detected in environmental monitoring samples. For example, all microorganisms recovered in the filling room should be routinely identified.

Also provide environmental monitoring and bioburden monitoring data including:

- A list of all lots of sterile **(b)(4)** produced by your firm since January 2015 and all bioburden tests performed. Annotate which lots were tested for bioburden and timing of each sample (**(b)(4)** sterilization or earlier in the process). Include all microbial count test results and state whether microbial identification was performed. If so, provide the identity of each microbe.
- A list of all environmental monitoring tests done for sterile **(b)(4)** production since January 2015, date of the sample, location sampled, and the identity of all isolated organisms.
- Your bioburden monitoring and testing procedures.

- A list of any out-of-specification results from bioburden or environmental monitoring testing and all original results and related investigations (if any result was re-tested or invalidated).

Additional guidance on aseptic processing
See FDA's guidance document, *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*, to help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing, at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf.

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 the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and evaluate the completion and effectiveness of corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

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 April 24, 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 Lernapharm (Loris) Inc. of 2323 Halpern St., Saint-Laurent, Montreal, 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 or mail your reply to:
Philip Kreiter
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 3004158845.

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