Corden Pharma Latina S.p.A. 5/20/16

Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Silver Spring, MD 20993

Via UPS
Return Receipt Requested
May 20, 2016

Warning Letter 320-16-14

Mr. Emilio Frongia
Corden Pharma Latina S.p.A.
Via del Murillo Km 2800
04013 Sermoneta
Italy

Dear Mr. Frongia:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Corden Pharma Latina S.p.A., Via del Murillo Km 2800, 04013 Sermoneta, Italy, from May 21–29, 2015.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, 21 CFR parts 210 and 211, and significant deviations from CGMP for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drugs 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 firm's June 19, 2015 response in detail and acknowledge receipt of your subsequent responses.

Our investigators observed specific violations and deviations including, but not limited to, the following.

Finished product violations

1. Your firm failed to have facilities used in the manufacture, process, packaging and holding of drug products of appropriate construction to facilitate cleaning, maintenance, and proper operations. (21 CFR 211.42(a))

We observed **(b)(4)** floor tiles (approximately **(b)(4)** by **(b)(4)**) in your sterile **(b)(4)** manufacturing area. Black grime and filth were visible in the tile **(b)(4)** throughout the aseptic area, including in the direct vicinity of the manufacturing equipment.Furthermore, cracked and inadequately repaired floor tiles created more gaps to hold filth.

In your response, you stated that you repaired cracked floor tiles and damaged seals in the **(b)(4)** room and under the **(b)(4)**, and replaced the flooring in the area of the aseptic filling machine.

Your response is inadequate. Floors should be **(b)(4)** where sterile products are manufactured. Smooth, hard surfaces that are easy to clean prevent accumulation of filth and discourage microbiological growth. There is no assurance that the repairs you made to the floors and the new tiles installed are adequate and appropriate for an aseptic processing facility. Specifically, there is no assurance that the repaired/replaced tile floors can ever be sufficiently cleaned and disinfected.

In your response to this letter, provide:

- A plan and timeline to replace the floors, including underneath heavy equipment, with a **(b)(4)** floor that is easy to clean and sanitize, without cracks and crevices. Send your plan and timeline before you install the new floors. Include your remediation actions for contaminants found under the tile floor. The remediation plan should include details regarding use of cleaners, sporicidal agents, and moisture removal.
- Your plan to requalify the facility after construction, including environmental qualification and media fill strategy.
- Photographic evidence after you complete the floor replacement to demonstrate that your facility meets CGMP requirements.

2. Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements. (21 CFR 211.67(a))

Your cleaning procedure includes spraying **(b)(4)** of water throughout the aseptic area. As a result, stagnant water collects underneath the aseptic filling machine. Stagnant water is a potential source of microbiological contamination, including biofilms and other filth.

According to your response, you are using a "**(b)(4)**-Mop" after cleaning to remove pools of water under the filling machine, and evaluating alternative disinfecting agents that will not require removal with water as a **(b)(4)** step. You did not demonstrate that the "**(b)(4)**-Mop" and new disinfectants are adequate for cleaning and sanitizing the floor.

After you have remediated your facility in line with the items above, update your cleaning procedures to ensure no stagnant water remains, and review all your

cleaning practices to ensure they do not increase the risk to the product for microbial or particulate contamination.

3. Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. (21 CFR 211.160(b))

You do not take samples for **(b)(4)** analysis from the **(b)(4)** bulk solution during routine commercial production. Instead you rely on sampling **(b)(4)** which does not provide meaningful results of **(b)(4)**.

According to your response, during process validation you sampled the **(b)(4)** bulk solution for **(b)(4)** to verify **(b)(4)** of the **(b)(4)**. However, you did not test the bulk drug solution **(b)(4)** to detect **(b)(4)** contamination.

(b)(4) test samples for aseptically-filled products should be taken **(b)(4)** steps to ensure that the **(b)(4)** data is reflective of the true in-process **(b)(4)** levels. Excess in-process **(b)(4)** levels can lead to **(b)(4)**, or other **(b)(4)** byproducts, that can **(b)(4)** and contaminate the finished product,

In your response to this letter, provide evidence that your **(b)(4)** testing regimen can detect **(b)(4)** contamination in **(b)(4)** bulk, and provide an updated procedure that stipulates that **(b)(4)** bulk drug solution **(b)(4)** analysis is required for each lot you produce.

API deviations

4. Your test procedures are not scientifically sound and appropriate to ensure that your API conform to established standards of quality and/or purity.

Your environmental monitoring data is not reliable. On May 27, 2015, our investigators observed 61 damaged **(b)(4)** plates during plate reading. Examples of damage included discolored **(b)(4)**, desiccated **(b)(4)** shrinking away from the edge of microbial plates, and **(b)(4)** that had completely detached and fallen onto the **(b)(4)** when **(b)(4)** during incubation.

(b)(4) that is desiccated, cracked, or damaged fundamentally compromises microbial growth promotion and accurate enumeration, and may result in the underestimation of microbiological counts and false negatives.

In your response, you evaluated each type of plate damage and concluded that the effects of plate damage are negligible, because microbiological growth on such **(b)(4)** is possible. This response is inadequate; use of deficient media fundamentally compromises the validity of your microbiological test results. Furthermore, you did not commit to stop using damaged plates for microbiological tests.

In your response to this letter, provide:

- An accelerated timeline for completing retroactive microbiological testing of all potentially-compromised batches via an independent laboratory, and a commitment to respond promptly with all OOS results.
- Your review of all microbiological test methods to ensure that they are suitable for their intended use.

5. The buildings and facilities used in the manufacture of your API are not designed and constructed to limit exposure to objectionable microbiological contaminants.

The floor of the sterile API aseptic processing area has multiple drains. In International Standards Organization Class 5 (ISO 5/Grade A) areas for aseptic filling, drains should not be used because of microbiological contamination risks.

In your response, there is insufficient scientific rationale for drains in the floor of your sterile API filling suite.

In response to this letter, provide your plan for removing drains from sterile API manufacturing areas.

CGMP Guidance

FDA's *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* guidance document may help you ensure that all aseptically-filled drug products meet standards for drugs purported to be sterile. Download from: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070342.pdf

Conclusion

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

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of drugs produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Staff immediately at drugshortages@fda.hhs.gov so that we can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances in the manufacture of your drugs under 21 U.S.C. 356C(a)(1), and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products. In appropriate cases, you may be able to take corrective action without interrupting supply, or to shorten any interruption, thereby avoiding or limiting drug shortages.

After you receive this letter, you have 15 working days to respond to this office in writing. Specify what you have done since our inspection to correct your violations and deviations and to prevent their recurrence.

If you cannot complete corrective actions within 15 working days, state your completion date and reasons for delay.

Until you completely correct all violations and deviations 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 and deviations may also result in FDA refusing admission of articles manufactured at Corden Pharma Latina S.p.A, Via del Murillo Km 2800, 04013 Sermoneta, Italy 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 within the meaning of section 501 (a)(2)(B) of the FD&C Act, 21 U.S.C. 351 (a)(2)(B).

Send your reply to:

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

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov

Please identify your response with FEI 3001229385.

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