Horizon Pharmaceuticals, Inc. 12/23/16

U.S. FOOD & DRUG ADMINISTRATION

Florida District
555 Winderley Place, Suite 200
Maitland, Florida 32751

VIA UPS NEXT DAY AIR
w/ DELIVERY CONFIRMATION

WARNING LETTER
FLA-17-06
December 23, 2016

Mr. Adam (Ehab) Ibrahim, CEO
Horizon Pharmaceuticals, Inc.
7880 Central Industrial Dr.
Riviera Beach, FL 33404-3452

Dear Mr. Ibrahim:

The U.S. Food and Drug Administration (FDA) inspected your Horizon Pharmaceuticals, Inc. drug manufacturing facilities in Riviera Beach, Florida: 971 W 15th Street (manufacturing and laboratory), and 7880 Central Industrial Drive (corporate headquarters, warehouse, media fill incubation room, and document storage), from October 27 to November 5, 2015.

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 November 28, 2015, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators 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)).

Your firm lacked appropriate controls to prevent contamination of your drug products.

Your sterility testing of Saljet (HPI-087) ophthalmic drug product lots 4J009, 4J010, and 4J011 manufactured in October, 2014 found that **(b)(4)** out of **(b)(4)** bottles were non-sterile. You identified the contaminating microbe as *Bacillus mycoides*. Although you lacked a scientific basis to invalidate these positive sterility results, you distributed all three lots based on a re-test.

Our inspection found multiple deficient practices at your facility that pose a significant microbiological contamination risk. For example, your cleaning and disinfection program lacked use of a sporicidal agent. Significantly, the microbe identified in the sterility failures is a spore-former. In addition, our inspection identified poor facility maintenance. This included leaking pipes in the cleanroom ceiling, chipped and cracked floors in the batch tank room, and blue and black particulates as well as dust on tanks next to the ingredient charging ports.

We acknowledge your commitment to improve your cleaning and sanitization program, including the addition of sporicidal agents to the program. However, a sound disinfectant program also includes a written schedule, sound methods, efficacy studies, and environmental data to support the ongoing effectiveness of the agents.

We also acknowledge your efforts to address the facility maintenance deficiencies cited in the inspection. However, your response lacks a commitment to fully assess the effectiveness of your overall facility and equipment maintenance program. Also, you did not commit to perform a comprehensive review of aseptic manufacturing operations to identify and address potential vulnerabilities in your operations that can pose a hazard to product sterility.

Your response should thoroughly address all of these issues. The comprehensive assessment of the sources of variability in your aseptic manufacturing facility and processing line should be accompanied by a corrective action and preventive action (CAPA) plan. Your response should also discuss whether other lots produced and released for distribution were impacted.

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 was already distributed (21 CFR 211.192).

a. Saljet (HPI-087)

Your firm identified contamination in **(b)(4)** out of **(b)(4)** bottles of Saljet (HPI-087) ophthalmic drug product comprising lots 4J009, 4J010, and 4J011, manufactured in October 2014. Without a meaningful scientific justification, your firm released these lots following a retest.

Your cursory investigation, and the subsequent batch release decision, was inadequate in that:

- No evidence of lab error was identified, or substantive explanation of a hypothetical fault in the laboratory analysis provided, to justify invalidation of the sterility positive test results.
- Negative controls yielded no growth.
- The investigation stated that "only" **(b)(4)** of **(b)(4)** tested units showed growth. It did not recognize that it is typical for contamination to be distributed non-uniformly in a batch.
- The investigation mentions that *Bacillus mycoides,* the same species found in the positive sterility tests, was isolated in your cleanrooms in October 2014 as part of environmental monitoring. However, the investigation did not recognize the significance of this direct correlation.
- The specific manufacturing process and facility conditions that could have led to the non-sterile lots were not thoroughly evaluated. No scientific rationale was provided to discount your production operation as the source of the microbial contamination.
- You did not include an evaluation of utility and/or support systems.
- You did not include a review of production history, including failures, deviations, qualification, validation, maintenance issues, and any major changes in operations.
- The lots were released following a re-test of additional units that yielded no additional positives.
- Your firm also failed to identify substantive corrective action and preventive actions.

Overall, there was a lack of management oversight to ensure a thorough investigation of these non-sterile batches, and prevent their distribution. We acknowledge your commitment to conduct a retrospective review for this failure.

In your response to this letter, provide conclusions from your comprehensive investigation, and discuss all other batches that may have been affected by the adverse conditions that caused the sterility failures. Provide a risk analysis on each of these batches.

Also include your site's media fill and sterility testing history since January, 2010. Whenever contamination was found, include the species identified. This summary should also include all instances in which any sterility test positive was invalidated or a positive media fill unit was disregarded, and a brief explanation behind this decision.

b. CMC Eye Drops (HPI-054)

Your investigation into failing stability results lacked scientific data and rationale. Our investigator found that, on November 17, 2014, 2 out of **(b)(4)** samples of 1% CMC Eye Drops (HPI-054) lot **(b)(4)** failed pouch integrity tests for stability at the **(b)(4)** interval.

Different analysts obtained both passing and failing results as they retested the **(b)(4)** samples multiple times. In investigation INV 15-001, you noted, "Although several pouch integrity test results were rejected due to failure, all remaining test results indicate there was no impact on the product..." You indicated that the foil "passed all test and inspections" and "[w]hen compared to other lots previously produced and placed on stability… there is not an increased risk that the product under test **(b)(4)**

will not maintain its pH value within the specified range throughout the shelf life of the products." You did not provide a scientific rationale to justify these conclusions.

At the **(b)(4)** interval on May 18, 2015, samples failed pouch integrity tests for stability again, but you did not investigate the OOS results.

Your response is inadequate because your firm lacks an adequate CAPA plan. Significantly, no remedial actions were taken when the **(b)(4)** stability samples failed the pouch integrity test. We acknowledge your proposal to improve your investigations by updating procedures. We note that you will also perform a **(b)(4)** retrospective review of all non-conformance reports (NCR) and CAPA to identify any "failure investigations" and to determine plausible potential root causes.

In response to this letter, provide:

- a scientifically sound rationale, including supporting documentation, for disregarding the **(b)(4)** pouch integrity stability tests
- a retrospective review of all laboratory tests, and an action plan for test results invalidated without adequate investigation
- an investigation of the **(b)(4)** pouch integrity stability test failures
- a list of all lots within expiration date, and a commitment to test each of these lots to determine if they have maintained their quality attributes (e.g., pH, assay) during shelf-life

c. *AVR eye drop vials*

In June, 2015, you discovered leaking product at the transfer plate to the Blow-Fill-Seal (BFS) machine in cleanroom **(b)(4)**. This was detected during aseptic production of Advanced Vision Research (AVR) eye drop vials lot #5S012. While you lacked clear evidence of when the leaks began and the filling line was compromised, you released a partial batch (**(b)(4)** cases).

You erroneously indicate that line overpressure prevents ingress of microorganisms when a piping connection is breached. You state that "the line is under a continuous positive pressure of **(b)(4)** PSI and the potential of microbial contamination ingress is unlikely due to general principles of physics." It is important that your firm recognize that any loss of integrity in a sterile line is a direct route of microbiological contamination. Such leaks pose an intolerable risk to the sterility of your ophthalmic products.

In your response, you indicated that you will improve your investigation procedures and that "[p]roduction line integrity failures will require sterilization-in-place [SIP] or a documented rationale for not performing SIP." Your response fails to provide adequate corrections.

In response to this letter:

- Provide your procedure for partial batch release. Also explain how and when a batch may be partially released.
- Provide retrospective investigation and risk analysis of all partial batch releases.
- Describe the maximum lot size and duration (processing time) permitted for all BFS operations. Include your maximum processing times between line sterilizations.
- Describe the size of sterility samples taken for each lot.

- Provide your assessment of all batches that may have been compromised by cleanroom leaks.
- Provide detailed information on the enhanced environmental monitoring sampling performed after completing the repair of your facility. Include data regarding microbes, including isolates of fungi and spore-forming bacteria, found in the area before and after the repairs.

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 drug products conform to appropriate standards of identity, strength, quality, and purity (21 CFR 211.160(b)).

Your visual inspection and test methods for filled vials are inadequate because they failed to demonstrate whether critical defects (such as particles) can be detected consistently. You lacked a specific viewing environment for the visual inspection process, including but not limited to:

- bright light for examination
- black/white viewing background
- written methods detailing what to look for physical or photographic examples of color, clarity, and particulate defects to which samples can be compared

Your written test method **(b)(4)** only states, “Visually inspect all test sample units for color, clarity, and visible particles.” It did not include the specific number of samples tested for each lot.

Your response is inadequate because it does not indicate how many samples will be tested or how many include relevant acceptance criteria. Furthermore, it does not indicate how you will qualify your staff to conduct visual inspections, or commit to review retains of lots still within expiry. However, we acknowledge your commitment to update all visual test procedures and train your employees.

In response to this letter, provide:

- your plans and associated reports evaluating the effectiveness of the new visual inspection procedure under actual conditions of use
- your results of a retrospective visual inspection analysis of retained samples of all drug products still within expiry

CGMP consultant recommended

Based upon the nature of the violations we identified at your firm, and your failure to correct repeat violations, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34, to assist your firm in meeting CGMP requirements. The consultant’s work should include, but not be limited to, a comprehensive evaluation of the suitability of your aseptic processing facilities and processes, and the sufficiency of management oversight of manufacturing and quality.

Your use of a consultant does not relieve your 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 in all your facilities.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA 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 or interruptions in your drug manufacture under 21 U.S.C. 356C(b) 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.

Correct the violations cited in this letter promptly. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Unresolved violations in this warning letter may also prevent other Federal agencies from awarding contracts.

Until these violations are corrected, we may withhold approval of pending drug applications listing your facility. We may re-inspect to verify that you have completed your corrective actions. We may also refuse your requests for export certificates.

After you receive this letter, respond to this office in writing within 15 working days. Summarize improvements made to your investigations and CAPA management procedures to ensure that your quality unit reviews each batch before release. Include your retrospective review of all failure investigations to ensure that your conclusions were scientifically justified. Provide a separate summary of investigations closed before you assigned a root cause.

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 business days, state your reasons for delay and your schedule for completion.

Send your reply to:

Randall L. Morris, Compliance Officer
FDA Florida District
U.S. Food and Drug Administration
555 Winderley Place, Suite 200
Maitland, FL 32751

Please identify your response with FEI 3000718824.

If you have questions regarding any issues in this letter, please contact Mr. Morris via email at Randall.Morris@fda.hhs.gov or by phone at (407) 475-4741.

Sincerely,
/S/
Susan Turcovski
District Director

Florida District