Opto-Pharm Pte Ltd. 3/16/17

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-17-30

March 16, 2017

Mr. Khoo Min
Managing Director
Opto-Pharm Pte Ltd.
13, Tuas Avenue 12
Singapore 639035
Republic of Singapore

Dear Mr. Khoo Min:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Opto-Pharm Pte Ltd. at 13, Tuas Avenue 12, Singapore, from March 14 to 22, 2016.

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 April 7, 2016, response in detail. You have not provided sufficient details or supporting evidence to demonstrate that you have taken adequate corrective actions.

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)).

During aseptic manufacturing of your sterile ophthalmic products **(b)(4)** (lot **(b)(4)**) and **(b)(4)** (lot **(b)(4)**), you documented numerous leaking containers and other bottle formation defects. To address these defects, you routinely adjusted your **(b)(4)** (**(b)(4)**) equipment and resumed production. You subsequently released these lots. Following distribution, you received customer complaints of leaking containers.

In addition, you found numerous critical container-closure defects, including leaking products, during media fills studies. Container integrity is imperative to ensure sterility of ophthalmic drug products. The lack of assurance that your **(b)(4)** equipment consistently manufactures an integral container-closure system diminishes confidence in the sterility of your marketed products.

Additionally, our inspection found that your firm re-uses **(b)(4)** as many as **(b)(4)** times before discarding them. **(b)(4)** should normally be used once, then discarded after manufacturing a single product lot. Repeated use and re-sterilization can compromise **(b)(4)** efficacy and physical/chemical stability (e.g., particles, leachables, extractables).

During our inspection, you acknowledged your failure to validate your process prior to distributing drugs. In your response, you committed to develop and execute protocols for process performance qualification and equipment qualification.

In response to this letter, provide the validation protocols and studies that evaluate whether your **(b)(4)** equipment is reliable. This includes but is not limited to determining whether your process reproducibly yields an integral container-closure system, and whether other process parameters and quality attributes are consistently met.

Also, by definition, a validated process operates in an ongoing state of control. It is essential that your firm improves your process design and control to correct the root causes of your recurring container-closure integrity defects. Without such remediation, successful process performance qualification studies alone are insufficient to demonstrate that your process is truly capable of a continuing state of control. In your response, provide an analysis of the root causes of in-process integrity defects and container-closure defects affecting distributed products. Also provide an update on all CAPA activities that have been undertaken to improve your process.

2. Your firm failed to establish the reliability of the container-closure supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals (21 CFR 211.84(d)(3)).

Your firm uses **(b)(4)** supplied by **(b)(4)** in your **(b)(4)** equipment to manufacture the container-closures for your ophthalmic products. You accepted values reported on the supplier's certificate of analysis for density and **(b)(4)** for each incoming lot but did not verify the reliability of the supplier's results.

Using **(b)(4)** that does not meet its quality attributes, such as density and **(b)(4)**, may result in container-closure integrity defects that could compromise the sterility of your ophthalmic drug products.

In your response, you committed to sending samples from **(b)(4)** batch of **(b)(4)** received to an external laboratory for density testing. You also committed to periodically evaluate your **(b)(4)** supplier. You did not provide justification for your acceptance criteria for the **(b)(4)**. In addition, you did not provide external laboratory results for density and **(b)(4)** values, or any supplier evaluations.

In response to this letter, provide justification to demonstrate your **(b)(4)** specifications are appropriate for the drug products you manufacture. Provide your supplier evaluations and a summary of laboratory test results relating to all of the components, containers, and closures you use to manufacture your sterile drug products.

3. Your firm failed to ensure that your drug products bore an expiration date that was supported by appropriate stability testing (21 CFR 211.137(a)).

Your firm failed to conduct stability studies for Buffered Saline and **(b)(4)** ophthalmic solutions produced in 2014 and 2015. Furthermore, at the time of the inspection, you could not provide raw data to support test results from stability studies you conducted for other products.

Your failure to conduct stability studies and lack of data supporting expiration dates compromises your ability to detect quality problems with marketed ophthalmic products. Without stability data, you cannot assure the quality of your products throughout their labeled shelf lives. In addition, you have received multiple customer complaints of leaking ophthalmic containers, which also calls into question your ability to maintain sterility of your ophthalmic products throughout their labeled expiration dates.

In your response, you commit to conducting stability studies on your Buffered Saline and **(b)(4)** products. However, you did not provide the raw stability data for other ophthalmic products.

In response to this letter, provide the following:

- raw stability data for all of your ophthalmic products manufactured for the U.S. market within expiry
- antimicrobial effectiveness testing that evaluates whether your products contain a suitable preservative system

- an evaluation of whether your products' preservative systems remain effective at their expiration dates

Buffered Eye & Skin: Unapproved New Drug Charges

The product labels for Buffered Eye & Skin Xpect and Buffered Eye & Skin First Aid Direct make claims that demonstrate the intended uses of the products. Please note that this is not an all-inclusive list of claims that demonstrate intended uses.

"For flushing the eye to remove loose foreign material or air pollutants (smog or pollen)"

Based on the above claim, Buffered Eye & Skin Xpect and Buffered Eye & Skin First Aid Direct are "drugs" as defined by section 201(g)(1)(B) of the FD&C Act [21 U.S.C. § 321(g)(1)(B)], because they are intended for the diagnosis, cure, mitigation, treatment, or prevention of disease, and/or under section 201(g)(1)(C) of the FD&C Act [21 U.S.C. § 321(g)(1)(C)] because they are intended to affect the structure or any function of the body of man.

Specifically, these products are intended as eyewashes. OTC drug products intended as eyewashes, such as Buffered Eye & Skin Xpect and Buffered Eye & Skin First Aid Direct, are subject to the final monograph for Ophthalmic Drug Products for Over-the-Counter Use, see 21 CFR Part 349. However, these products are not labeled or formulated in accordance with this final monograph. While the labeled indications for Buffered Eye & Skin Xpect and Buffered Eye & Skin First Aid Direct state that the products are intended for flushing the eye, the product names "Buffered Eye & Skin" suggest that the products are intended for flushing the eye and skin. However, this intended use (e.g. flushing the skin) is not a permitted indication in the final monograph for eyewash drug products, see 21 CFR 349.78(b).

Thus, as formulated and labeled, Buffered Eye & Skin Xpect and Buffered Eye & Skin First Aid Direct do not comply with the final monograph described above. Furthermore, we are not aware of sufficient evidence to show Buffered Eye & Skin Xpect and Buffered Eye & Skin First Aid Direct, as formulated and labeled, are generally recognized as safe and effective. Therefore, these products are new drugs within the meaning of Section 201(p) of the FD&C Act [21 U.S.C. § 321(p)] because they are not generally recognized among scientific experts as safe and effective for their labeled uses.

As new drugs, Buffered Eye & Skin Xpect and Buffered Eye & Skin First Aid Direct may not be legally marketed in the United States absent approval of an application filed in accordance with Section 505 of the FD&C Act [21 U.S.C. § 355(a)]. Buffered Eye & Skin Xpect and Buffered Eye & Skin First Aid Direct are not the subject of FDA-approved applications, and therefore, the current marketing of these products violate section 505(a) of the FD&C Act [21 U.S.C. § 355(a))]. Introduction of such products into interstate commerce is prohibited under Section 301(d) of the FD&C Act [21 U.S.C. § 331(d)].

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 http://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. 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.

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.

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 Opto-Pharm, 13, Tuas Avenue 12, Singapore, 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 3005320466.

Sincerely,
/S/
Thomas J. Cosgrove
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research