WARNING LETTER

Altaire Pharmaceuticals, Inc.

MARCS-CMS 586153 — MARCH 12, 2020

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Mr. Assad S. Sawaya

President & CEO

Altaire Pharmaceuticals, Inc.

P.O. Box 849
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United States

Issuing Office:

Division of Pharmaceutical Quality Operations I

United States

Warning Letter
CMS # 586153

March 12, 2020

Dear Mr. Sawaya:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Altaire Pharmaceuticals, FEI 1000119582, at 311 W Ln, Aquebogue, New York, from March 25 to April 19, 2019.

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 May 10, 2019, response in detail and acknowledge receipt of your subsequent correspondence. We also acknowledge that you initiated a recall and you committed to cease operations for certain drug products, on June 21, 2019.

During our inspection, our investigators observed specific violations including, but not limited to, the following.

1. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

Your firm manufactures sterile ophthalmic drug products which are subject to approved FDA applications for human and veterinary drug products. Additionally, your firm manufactures sterile ophthalmic over-the-counter (OTC) and homeopathic drug products.

Our inspection revealed serious data integrity breaches and other serious violations relating to environmental and personnel monitoring.

We found that plates taken from ISO 5 areas exceeded action limits, but your firm failed to initiate investigations.

Furthermore, laboratory technicians falsified this data which is critical to maintaining an ongoing state of control in your aseptic processing facility. For instance, an environmental monitoring plate was recorded by your technician as "0" on your viable surface monitoring report form. The discarded plate was retrieved that same day and observed to contain colonies too numerous to count.

In addition, although you failed to conduct "post activity" personnel monitoring for up to a year, your technicians repeatedly recorded results of "0" on the personnel **(b)(4)** report form. Personnel monitoring samples are critical because they indicate whether or not personnel in the aseptic processing environment are adversely affecting quality.

Due to this lack of authentic data relating to the microbial control of personnel who perform aseptic processing operations, you lacked information that is basic to determining aseptic processing control. For up to a year, you lacked the ability to identify microbial contamination risks posed by personnel.

Your failure to reliably record data, the systemic flaws that led to these fundamental data integrity breaches, and your lack of sufficient investigations into both, raises questions regarding integrity of data throughout your operation.

In your response, you stated that you opened an investigation into these serious violations and you "believe the issues of environmental monitoring and personnel monitoring occurred over the past twelve months." You stated that your "QC-microbiology lab immediately ceased the recording of Post-Activity results if such sampling was not performed." As a part of your investigation, you interviewed microbiologists who were responsible for personnel monitoring. These employees stated that a prior supervisor and a prior lab technician had instructed them to conduct only pre-activity sampling but to complete all the spaces on the personnel **(b)(4)** report form. This included recording "post activity" results, although the microbiological tests were not actually performed.

In your response you committed to engaging third-party consultants to assist with the remediation of your facility. You also conducted formal remedial training for the QC Microbiology department personnel. However, your response lacked adequate detail of how you retrospectively evaluated the scope and causes of your environmental monitoring and personnel monitoring data breaches. Although you stated you would establish and implement good documentation practices and data integrity procedures, you failed to address the pervasive nature of your firm's practices of creating unreliable records and your lack of a quality culture.

In your response to this letter, provide the following:

• A complete, independent assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed corrective action and preventive action (CAPA) plan that comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate, and contemporaneous records throughout your operation.

• A comprehensive, independent assessment of your firm's environmental monitoring and personnel monitoring programs, including both the adequacy of the entire written program and its actual practices. Provide a thorough CAPA plan, including but not limited to a commitment for procedures to require photographs of all environmental/personnel monitoring plates in the future.

• A retrospective review of microbiology test results. Provide all details you have been able to amass regarding environmental/personnel monitoring samples found to contain colonies outside action levels and all out-of-specification (OOS) microbiological results from January 2018 to the date of this letter.
o Include all results, including those that were falsified, misreported, or invalidated. Detail your investigations into, and retrospective evaluations of, the root causes of OOS tests or microbiological excursions in your manufacturing operation.

• A comprehensive assessment of your overall system for investigating deviations, discrepancies, complaints, OOS results, and failures. Provide a detailed CAPA plan to remediate this system. Your CAPA plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, quality assurance oversight, and written procedures. It should also address how you will ensure all phases of an investigation are appropriately conducted and the CAPA is effective.

• Provide comprehensive remediation to address each item listed in the section below entitled "Data Integrity Remediation." Place special emphasis on describing the following in great detail:
o The scope of the issues in the microbiology laboratory as well as across your firm's chemistry laboratory and production areas, including but not limited to the 12-month period you refer to in your response.
o A detailed list and assessment of each of the data integrity deficiencies that occurred with respect to environmental and personnel monitoring, as well as any other deviations identified by your further evaluation and remediation efforts.

2. 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 falsified laboratory data used to make batch release decisions for sterile ophthalmic drug products. In addition, you did not perform a required **(b)(4)** test to determine whether **(b)(4)** contained viable microorganisms. Your firm released these products to the market despite the lack of accurate and reliable analyses for products purporting to be sterile.

Specifically, your laboratory technicians recorded no growth ("NG") for **(b)(4)** of sterility test media that were observed during the inspection to be turbid. Although **(b)(4)** were found to be turbid, you did not deem the product to be non-sterile or perform the additional **(b)(4)** step that is critical if a **(b)(4)** inherent turbidity issue is suspected. Regarding the latter, if a laboratory suspects that the turbidity could be of a non-microbial nature, **(b)(4)** is performed to ensure that such inherent turbidity is not masking microbial growth. Notably, your firm's procedure **(b)(4)**.

Your firm believes deficient laboratory practices relating to preparation of both of the sterility test media led to the turbid appearance of sterility test canisters. You stated that at the time of the inspection "**(b)(4)** was not prepared to be particulate free" and that the **(b)(4)** sometimes appeared with tiny black particulates." You "determined that the source of such was overheating the glassware which burned some of the medium at the bottom of the vessels." Your response stated that you will formalize a procedure for "when and how to perform **(b)(4)**."

We also note that you committed to have all products currently within expiry sterility tested by outside laboratories. Note that finished product sterility testing has limitations: it does not, on its own, establish the sterility of all units in a given batch because contamination is not normally uniformly distributed. Examples of

other essential information to be evaluated along with the sterility test include data on the capability of the process to produce a sterile product, as well as data on the facility and process conditions associated with a given cycle of batch production.

In addition, the method suitability data you submitted for your contract lab, **(b)(4)**, was insufficient. It is your responsibility to ensure contract laboratories are qualified, including but not limited to their use of methods and equipment that are validated and suitable for the analysis of your drug products.

In response to this letter, provide the following:

• A comprehensive, independent review of your laboratory practices, procedures, methods, equipment, and analyst competencies (for both microbiology and chemistry laboratories). Based on this review, provide a detailed CAPA plan to fully remediate your laboratory system. Your plan should also include the process you will use to evaluate the effectiveness of the implemented CAPA. If a contract facility will be performing any laboratory functions on your behalf, conduct the same comprehensive assessment, implement an appropriate supplier CAPA, and provide a summary of your activities.

• A comprehensive third-party report that thoroughly evaluates all microbiological test methods and includes a CAPA for all deficiencies found.

• A commitment to notify FDA when or if your firm's laboratory resumes sterility testing of your products.

3. Your firm failed to ensure that manufacturing personnel wear clothing appropriate to protect drug product from contamination (21 CFR 211.28(a)).

Improperly gowned operators were observed performing aseptic operations that could place products at high risk for contamination. For example:

• Non-individually wrapped gloves used in aseptic operations are **(b)(4)** sterilized by your firm. Operators retrieve these gloves from the bulk container prior to entering the aseptic core, compromising the sterility of the gloves.

• Three operators observed during manufacturing in a cleanroom had exposed skin, including foreheads, noses, and sides of faces due to ill-fitting hoods and goggles.

In your response, you stated that you are in the process of sourcing **(b)(4)** gloves and new hoods with better head coverage. You are performing gowning qualifications.

You also stated that you opened an investigation for the drug product lot manufactured on March 25, 2019, including a review of personnel bioburden and environmental data for any potential product impact. However, you failed to address how your inadequate gowning practices impacted other batches of drug products.

In response to this letter, provide your plan to ensure appropriate aseptic practices and cleanroom behavior during production. Include steps to ensure routine and effective supervisory oversight for all production batches. Also describe the frequency of quality unit oversight (e.g., audit) during aseptic processing and other operations.

4. 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 media fill program lacked sufficient assessment of process risks and an adequate record of the nature of simulated interventions. For example, the media fill batch records did not incorporate a representative number, type, and complexity of routine interventions that occurred with each run, nor did they include nonroutine interventions and events (e.g., maintenance and equipment adjustments). If a media fill program fails to incorporate contamination risk factors that closely simulate actual drug product exposure, the state of process control and sterility assurance cannot be accurately assessed.

Furthermore, you failed to perform **(b)(4)** media fills to evaluate the state of control of the aseptic process. Specifically, **(b)(4)** aseptic processing rooms failed to have at least **(b)(4)** media fills conducted as required by your SOP. Additionally, no media fills were conducted in at least two rooms for an entire year.

In your response, you committed to reviewing historical media fill study data to identify any re- qualifications that were not performed. You also stated that you would re-qualify the line in cleanroom **(b)(4)**.

However, your response failed to address how these major deficiencies in your media fill program affect the level of confidence in ongoing aseptic production capability. In addition, although you stated you would begin constructing a media fill timeline for the remainder of 2019, you did not commit to immediately performing adequate media fills to accurately assess the state of control of operations and to evaluate the sterility of drug products.

In your response to this letter, provide the following:

• A comprehensive, independent third-party review of your media fill program.

• A CAPA plan, with timelines, to address the findings of the independent review.

• A commitment to **(b)(4)** media fills for each aseptic processing line (**(b)(4)**).

• An overall management strategy that describes how your production and quality management will better oversee design and execution of manufacturing and ensure routine scrutiny to support an ongoing state of control.

5. Your firm failed to use equipment in the manufacture, processing, packing, or holding of drug products that is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance (21 CFR 211.63).

Equipment was not properly maintained and readily cleanable. During our inspection, we observed aluminum foil and duct tape attached to equipment on your filling line. Your production staff stated that your firm used the aluminum foil to prevent bottle tops from falling from the hopper. In addition, **(b)(4)** in your cleanroom and a portable cart containing a **(b)(4)** were observed to be stained.

In your response, you stated that the maintenance department, under oversight of the Quality Assurance Department, will remove the tape and foil fastened to the hopper in **(b)(4)**, and identify the issue causing the bottle tops to fall. You also said you would replace the **(b)(4)** for the portable cart and determine if the stained **(b)(4)** in the cleanroom were functioning within their limits. However, you failed to provide a detailed plan for comprehensive assessment of the design, control, and maintenance of your aseptic processing lines and cleanrooms.

In your response to this letter, provide the following:

• A comprehensive, third-party risk assessment of all contamination hazards with respect to your aseptic processes, equipment, and facilities, including, but not limited to:
o All human interactions within the ISO 5 area
o Equipment placement and ergonomics
o Air quality in the ISO 5 area and surrounding room
o Facility layout
o Personnel Flows and Material Flows (throughout all rooms used to conduct and support sterile operations)

• A detailed CAPA plan with timelines to address the findings of the contamination hazards risk assessment. Describe how you will improve aseptic processing operation design and control.

• Your CAPA plan to implement routine, vigilant operations management oversight of facilities and equipment. This plan should ensure, among other things, prompt detection of equipment/facilities performance issues, effective execution of repairs, adherence to appropriate preventive maintenance schedules, timely technological upgrades to the equipment/facility infrastructure, and improved systems for ongoing management review.

• Your new **(b)(4)** report for all aseptic processing lines

Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document *Data Integrity and Compliance With Drug CGMP* for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/media/97005/download (https://www.fda.gov/media/97005/download).

We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements. We strongly recommend that you retain a qualified consultant to assist in your remediation.

In response to this letter, provide the following:

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting including all data deficiencies that were submitted to FDA as part of applications that ultimately were approved based on your firm's review and release of this data. Your investigation should include:
o A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
o Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
o An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
o A comprehensive retrospective evaluation of the nature of the manufacturing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include:
o A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all the data you generate including analytical data, manufacturing records, and all data submitted to FDA.
o A comprehensive description of the root causes of your data integrity lapses including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.
o Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
o Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
o A status report for any of the above activities already underway or completed.

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 CGMP requirements when manufacturing sterile drugs using aseptic processing, at https://www.fda.gov/media/71026/download (https://www.fda.gov/media/71026/download).

Consultant

You have committed to hiring a consultant. Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations 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 that the consultant evaluates the completion and efficacy of your 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 resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

Repeat Observations

In March 9, 2017, December 15, 2015, and August 8, 2013, inspections, FDA cited similar CGMP observations. You proposed specific remediation for these observations in your response. Repeated failures demonstrate that executive management oversight and control over the manufacture of drugs is inadequate.

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 (drugshortages@fda.hhs.gov), and the Center for VeterinaryMedicine (CVM) at AskCVM@fda.hhs.gov (AskCVM@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. 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 response to orapharm1_responses@fda.hhs.gov. Your written notification should refer to the Warning Letter Number above CMS # 586153.

If you have any questions, contact Compliance Officer BarbaraWilimczyk-Macri at barbara.wilimczyk@fda.hhs.gov or 973-331-4951.

Sincerely,

/S/

Diana Amador-Toro
Program Division Director
Office of Pharmaceutical Quality Operations Division I

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