Atlas Pharmaceuticals, LLC 9/11/18

WARNING LETTER

VIA SIGNATURE CONFIRMED DELIVERY

September 11, 2018

Nancy J. Costlow, PharmD, RPh
Director
Atlas Pharmaceuticals, LLC
711 E. Carefree Highway, Suite 107
Phoenix, Arizona 85085-0101

Dear Dr. Costlow:

You registered with the U.S. Food and Drug Administration (FDA) as an outsourcing facility under section 503B of the Federal Food, Drug, and Cosmetic Act (FDCA) [21 U.S.C. § 353b] ***[1]*** on November 8, 2016, and most recently on November 8, 2017. From August 15, 2017, through September 26, 2017, an FDA investigator inspected your facility, Atlas Pharmaceuticals, LLC, located at 711 E. Carefree Highway, Suite 107, Phoenix, Arizona 85085-0101. During the inspection, the investigator noted that drug products you produced failed to meet the conditions of section 503B of the FDCA necessary for drugs produced by an outsourcing facility to qualify for exemptions from certain provisions of the FDCA. In addition, the investigator noted serious deficiencies in your practices for producing sterile drug products, which put patients at risk.

FDA issued a Form FDA 483 to your facility on September 26, 2017. FDA acknowledges receipt of your facility's response, dated October 16, 2017. Based on this inspection, it appears you produced drugs that violate the FDCA.

A. Compounded Drug Products under the FDCA

Under section 503B(b) of the FDCA, a compounder can register as an outsourcing facility with FDA. Drug products compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility qualify for exemptions from the drug approval requirements in section 505 of the FDCA [21 U.S.C. § 355(a)], the requirement in section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)] that labeling bear adequate directions for use and the Drug Supply Chain Security Act requirements in section 582 of the FDCA [21 U.S.C. § 360eee-1] if the conditions in section 503B of the FDCA are met.***[2]***

An outsourcing facility, which is defined in section 503B(d)(4) of the FDCA [21 U.S.C. § 353b(d)(4)], is a facility at one geographic location or address that — (i) is engaged in the compounding of sterile drugs; (ii) has elected to register as an outsourcing facility; and (iii) complies with all of the requirements of this section. Outsourcing facilities must comply with other applicable provisions of the FDCA, including section 501(a)(2)(B) [21 U.S.C. § 351(a)(2)(B)], regarding current good manufacturing practice (CGMP), and section 501(a)(2)(A) [21 U.S.C. § 351(a)(2)(A)], regarding insanitary conditions. Generally, CGMP requirements for the preparation of drug products are established in Title 21 of the Code of Federal Regulations (CFR) parts 210 and 211.

For a compounded drug product to qualify for the exemptions under section 503B, the labeling of the drug must include certain information (section 503B(a)(10) of the FDCA [21 U.S.C. §353b(a)(10)]).

B. Failure to Meet the Conditions of Section 503B

During the inspection, an FDA investigator noted that drug products produced by your facility failed to meet the conditions of section 503B. Specifically, the investigator noted that some of your facility's drug products did not include the following statement on the labels: the statement, "Not for resale." Further, some of your facility's drug product labels included the following statement, "This is a compounded preparation," instead of the required, "This is a compounded drug," statement.

Because your compounded drug products have not met all of the conditions of section 503B, they are not eligible for the exemptions in that section from the FDA approval requirements of section 505, the requirement under section 502(f)(1) that labeling bear adequate directions for use, and the Drug Supply Chain Security Act requirements described in section 582 of the FDCA.

Specific violations are described below.

C. Violations of the FDCA

Adulterated Drug Products

The FDA investigator noted that drug products intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, the investigator noted that:

1. Your firm failed to perform adequate smoke studies under dynamic conditions to demonstrate unidirectional airflow within the ISO 5 area. Therefore, your products intended to be sterile are produced in an environment that may not provide adequate protection against the risk of contamination.

2. Your firm failed to disinfect equipment and supplies upon transferring them from areas of lower air quality to areas of higher air quality. Specifically, an employee was observed transporting materials used in sterile drug production from an ISO-8 classified room to an ISO-7 classified room without disinfecting the materials.

3. Your firm produced commercial drug products prior to the successful completion of your media fill simulations. In addition, one of your media fill lots included a failure due to microbial growth. Therefore, your products may be produced in an environment that poses a significant contamination risk.

4. Your firm failed to use a sporicidal agent as part of your disinfection program for the aseptic processing areas.

The FDA investigator also noted CGMP violations at your facility, that caused your drug product(s) to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations include, for example:

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)).

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).

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

4. Your firm failed to establish an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions (21 CFR 211.42(c)(10)(v)).

5. 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)).

6. 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)).

7. Your firm failed to prepare batch production and control records with complete information relating to the production and control of each batch of drug product produced (21 CFR 211.188).

Outsourcing facilities must comply with CGMP requirements under section 501(a)(2)(B) of the FDCA. FDA's regulations regarding CGMP requirements for the preparation of drug products have been established in 21 CFR parts 210 and 211. FDA intends to promulgate more specific CGMP regulations for outsourcing facilities. FDA has issued a draft guidance, *Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act*. This draft guidance, when finalized, will describe FDA's expectations regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 until more specific CGMP regulations for outsourcing facilities are promulgated.

It is a prohibited act under section 301(k) of the FDCA [21 U.S.C. § 331(k)] to do any act with respect to a drug, if such act is done while the drug is held for sale after shipment in interstate commerce and results in the drug being adulterated.

Misbranded Drug Products

You compound drug products that are intended for conditions not amenable to self-diagnosis and treatment by individuals who are not medical practitioners; therefore, adequate directions for use cannot be written so that a layman can use these products safely for their intended uses. Consequently, their labeling fails to bear adequate directions for their intended uses causing them to be misbranded under section 502(f)(1) of the FDCA.***[3]*** It is a prohibited act under section 301(k) of the FDCA to do any act with respect to a drug, if such act is done while the drug is held for sale after shipment in interstate commerce and results in the drug being misbranded.

D. Corrective Actions

We have reviewed your firm's October 16, 2017, response to the Form FDA 483.

Regarding the insanitary conditions and CGMP observations observed during this inspection, some of your corrective actions appear inadequate.

1. Your response states that you have revised your written procedures, in part, to clarify investigation documentation requirements and to describe procedures for repeating a media fill following a [media fill] failure. However, it does not address the implications of producing and releasing a batch of sterile drug product without validating the aseptic process used for its production. Additionally, you did not include a copy of the investigation procedure for evaluation.

2. Your response states that Batch # S-60008 was produced over **(b)(4)**, and that you had viable air and surface sample results on the day the "sterile fill" was performed. You also state gloved fingertip sampling was performed on the dates of each media fill and batch production. However, your batch production records and Routine Fingertip Sampling Form do not support these assertions. For example, production records for Batch # S-60008 indicate it was produced on June 22, 2017; however, your environmental monitoring log indicates no viable air or surface sampling was conducted that day.

We are unable to fully evaluate the following corrective actions due to a lack of adequate supporting documentation. Specifically:

1. Your response states that you revised SOP # S-09, in part, to describe "dynamic" operations, and notes smoke studies were repeated in September 2017 to better simulate actual production activities. However, you did not include an updated copy of SOP # S-09 or a report detailing the outcome of smoke studies conducted in September 2017.

2. Your response acknowledges an operator failed to follow existing procedures in not disinfecting materials when transferring them from an area of lower quality air to an area of higher quality air. However, you did not include a copy of SOP # S-13, titled "*Sterile Environment and Processing Specifications*." Your response also indicates an

investigation was subsequently conducted, which resulted in the lot of drug product associated with this event (i.e. Lot # **(b)(4)**) being "*disposed of*." However, you did not include a copy of the investigation report or any documentation verifying the destruction of the lot of drug product.

3. Your response indicates that sterilization and depyrogenation procedures and protocols have been either implemented or revised. However, you did not include any of the procedures, protocols, or reports to verify the adequacy of your corrective actions.

4. In response to the observation that your media fills (i.e., process simulations) are inadequate, you state that your procedures and associated records (i.e., batch records and logs) have been updated. However, you did not include any of these documents for review.

5. Your response states that you have implemented SOP # Q-26 "*Assigning Lot Numbers*" to conform with USP's standards for assigning expiration dates to **(b)(4)**." However, you did not include a copy of the written procedure for evaluation.

6. Your response notes that you have updated written procedures and implemented the use of a log to document equipment/instrument cleaning & maintenance. However, you did not include any documentation for evaluation.

7. Your response states that you have updated SOP # Q-25 "Batch Record Control, Usage and Issuance" to improve documentation practices. However, you did not include a copy of the written procedure for evaluation.

In addition to the issues discussed above, you should note that CGMP requires the implementation of quality oversight and controls over the manufacture of drugs, including the safety of raw materials, materials used in drug manufacturing, and finished drug products. *See* section 501 of the FDCA. If you choose to contract with a laboratory to perform some functions required by CGMP, it is essential that you select a qualified contractor and that you maintain sufficient oversight of the contractor's operations to ensure that it is fully CGMP compliant. Regardless of whether you rely on a contract facility, you are responsible for assuring that drugs you produce are neither adulterated nor misbranded. [*See* 21 CFR 210.1(b), 21 CFR 200.10(b).]

In addition, regarding observations related to the conditions of section 503B of the FDCA, your corrective actions to your labels appear to be adequate. Specifically, you provided a corrected label for Ascorbic Acid 500mg/mL that includes the statement, "Not for resale," and "This is a compounded preparation."

FDA strongly recommends that your management undertake a comprehensive assessment of operations, including facility design, procedures, personnel, processes, maintenance, materials, and systems. In particular, this review should assess your aseptic processing operations. A third-party consultant with relevant sterile drug manufacturing expertise should assist you in conducting this comprehensive evaluation.

E. Conclusion

The violations cited in this letter are not intended to be an all-inclusive statement of violations at your facility. You are responsible for investigating and determining the causes of the

violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to ensure that your firm complies with all requirements of federal law, including FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure and injunction.

Within fifteen (15) working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Please include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you do not believe that the products discussed above are in violation of the FDCA, include your reasoning and any supporting information for our consideration. If you cannot complete corrective action within fifteen (15) working days, state the reason for the delay and the time within which you will complete the correction.

Your written notification should refer to the Warning Letter Number above (**564139**). Please address your written response to:

CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV
U.S. Food & Drug Administration
19701 Fairchild
Irvine, California 92612-2506

If you have questions regarding the contents of this letter, please contact Mariza Jafary via email at Mariza.Jafary@fda.hhs.gov or by telephone at 949-608-2977 and reference unique identifier number **564139**.

Sincerely,
/S/
CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV

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[1] *See* Pub. L. No. 113-54, § 102(a), 127 Stat. 587, 587-588 (2013).

[2] We remind you that there are conditions, other than those discussed in this letter, that must be satisfied to qualify for the exemptions in section 503B of the FDCA.

[3] Your compounded drug products are not exempted from the requirements of section 502(f)(1) of the FDCA by regulations issued by the FDA (see, e.g., 21 CFR 201.115).