Fusion IV Pharmaceuticals, Inc. dba Axia Pharmaceutical 2/21/18

Division of Pharmaceutical
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WARNING LETTER

VIA SIGNATURE CONFIRMED DELIVERY

February 21, 2018

Navid Vahedi, Owner
Fusion IV Pharmaceuticals, Inc.
dba Axia Pharmaceutical
1990 Westwood Blvd, Suite 135
Los Angeles, California 90025-4560

Dear Dr. Vahedi:

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 January 6, 2017. From March 13, 2017, to March 23, 2017, U.S. Food and Drug Administration (FDA) investigators inspected your facility, Fusion IV Pharmaceuticals, Inc. dba Axia Pharmaceutical, located at 1990 Westwood Blvd, Suite 135, Los Angeles, CA 90025-4560. During the inspection, the investigators 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 investigators 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 March 23, 2017. FDA acknowledges receipt of your facility's response, dated April 12, 2017, and your subsequent submission dated May 12, 2017. We also acknowledge your firm's voluntary recall, initiated on July 12, 2017, of **(b)(4)** (Lot # **(b)(4)**) due to current good manufacturing practices (CGMP) deviations. Based on this inspection, it appears you produced drugs that violate the FDCA.

A. Compounded Drug Products under the FDCA

The Drug Quality and Security Act (DQSA) was enacted on November 27, 2013. Title I of the DQSA, the Compounding Quality Act (CQA), added a new section 503B to 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, bulk drug substances used to compound it must appear on a list established by the Secretary identifying bulk drug substances for which there is a clinical need ("503B bulks list"), or that appear on the drug shortage list in effect under section 506E of the FDCA at the time of compounding, distribution, and dispensing (section 503B(a)(2)(A)(i) of the FDCA [21 U.S.C. § 353b(a)(2)(A)(i)]).

In addition, 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)]).]

Further, for a compounded drug product to qualify for the exemptions under section 503B, it must be compounded in an outsourcing facility that is in compliance with the registration and reporting requirements in section 503B(b) including the requirement to submit a report to FDA upon initially registering as an outsourcing facility, once in June of each year, and once in December of each year identifying the drug products compounded during the previous 6-month period (section 503B(b)(2) of the FDCA [21 U.S.C. §353b(b)(2)]).

B. Failure to Meet the Conditions of Section 503B

During the inspection, FDA investigators noted that drug products produced by your facility failed to meet the conditions of section 503B. For example, the investigators noted:

1. Your facility compounded drug products **(b)(4)**. Drug products compounded using these bulk drug substances are not eligible for the exemptions provided by section 503B, because they do not appear on the 503B bulks list, and are not used to compound a drug that appears on the drug shortage list.[3]

2. Some of your facility's drug products that you dispensed or distributed other than pursuant to a prescription for an individually identified patient did not include the statement "Office Use Only" on the label. Additionally, some of your facility's drug products did not include the following information on the container to facilitate adverse event reporting: www.fda.gov/medwatch and 1-800-FDA-1088.

3. Your facility failed to submit a report to FDA upon initially registering as an outsourcing facility in January 2017, and also failed to submit reports in June 2017 and December 2017, identifying the drug products that you compounded during the previous 6-month period.

Because your compounded drug products have not met all of the conditions of section 503B, they are not eligible for the exemptions 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

FDA investigators 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 investigators noted that your firm continued to produce commercial products prior to the successful completion of your media fill validation protocol, which included **(b)(4)** media fill failures due to **(b)(4)** and turbidity of growth media. Your firm also failed to perform media fills for your automated vial filling machine, which has been used to **(b)(4)** fill sterile drug products for commercial production. In addition, the investigators found that your firm failed to demonstrate through appropriate studies that the room containing your automated vial filling machine is able to provide adequate protection of the ISO 5 area in which sterile products are processed. Therefore, your products may be produced in an environment that poses a significant contamination risk.

FDA investigators 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 does not have, for each batch of drug product purporting to be sterile and/or pyrogen-free, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product. (21 CFR 211.167(a))

3. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of such stability testing to determine appropriate storage conditions and expiration dates. (21 CFR 211.166(a))

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 FDAC*. 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.

Under section 301(a) of the FDCA [21 U.S.C. § 331(a)], the introduction or delivery for introduction into interstate commerce of any drug that is adulterated is a prohibited act. Further, 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.

Unapproved New Drug Products

You do not have any FDA-approved applications on file for drug products that you compound.[4] Under sections 505(a) and 301(d) and of the FDCA [21 U.S.C. §§ 331(d)] a new drug may not be introduced into or delivered for introduction into interstate commerce unless an application approved by FDA under section 505 of the FDCA is in effect for the drug. Marketing of these products, or other applicable products, without an approved application violates these provisions of the FDCA.

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.[5] The introduction or delivery for introduction into interstate commerce of these products therefore violates section 301(a) of the FDCA. It is also 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.

Failure to Report Drugs

FDA acknowledges receipt of your interim product report on March 23, 2017. As noted above, however, your facility failed to submit a report to FDA upon initial registration as an outsourcing facility in January 2017, and again in June 2017, identifying the drug products that you compounded during the previous 6-month period (section 503B(b)(2) of the FDCA). The failure to report drugs by an entity that is registered with FDA in accordance with section 503B(b) is a prohibited act under section 301(ccc)(3) of the FDCA [21 U.S.C. § 331(ccc)(3)].

D. Corrective Actions

We have reviewed your facility's responses to the Form FDA 483. We also acknowledge your firm's voluntary recall, initiated on July 12, 2017, of **(b)(4)** (Lot #**(b)(4)**) due to CGMP deviations.

The following corrective actions appear to be deficient:

1. Your response and aseptic process simulation (APS) trial final reports do not adequately demonstrate a consistent ability to maintain aseptic operating conditions. The response does not indicate if your firm has evaluated impact to drug products that were made and distributed prior to the completion of the validation runs. In addition, your firm failed to investigate particulates identified in media fill runs deemed "successful."

2. Your response does not address the lack of growth promotion testing data to support the viability of media that you prepare outside of the instructions specified by the media manufacturer.

3. Your response does not address any potential impact to product quality from the **(b)(4)** sterilization cycle (**(b)(4)**) for **(b)(4)** products following the re-execution of the **(b)(4)** PQ. In addition, you provided no data or justification supporting your determination that the **(b)(4)** results are reliable for previously released batches of products sterilized using the **(b)(4)** cycle.

4. Your response states that method suitability testing of the **(b)(4)** is underway. However, your firm continues to release product without a validated sterility test method.

We are unable to fully evaluate some of your corrective actions due to the lack of adequate supporting documentation:

1. You state that you have run aseptic process simulation trials for the automated filling machine, but insufficient documentation has been provided to demonstrate their completion. Furthermore, it is unclear whether the planned media fills will simulate routine aseptic production as the **(b)(4)** validation run batch record submitted includes **(b)(4)** sterilizing the product in an **(b)(4)** after filling **(b)(4)** drug

product lots produced on the automated filling machine between **(b)(4)** were not **(b)(4)** sterilized.

2. You submitted the report of smoke pattern testing of the ISO 5 Filler Room; however, the response cannot be fully evaluated due to the lack of details regarding simulated operations during the smoke study. The vendor report does not outline the **(b)(4)** in the filling room, **(b)(4)**, or **(b)(4)** during the smoke study.

3. Your response related to antimicrobial effectiveness studies does not include sufficient documentation for us to fully evaluate your proposed corrective actions. Specifically, the new procedure provides a method for **(b)(4)** testing, but the response provides no context for its use. In addition, the new **(b)(4)** testing procedure is unclear in the instructions for testing.

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 based upon our review of the revised labels submitted in your Form FDA 483 response, dated April 12, 2017.

Regarding observations related to the product reporting requirements under section 503B of the FDCA, we acknowledge your submission of an interim report dated March 23, 2017. However, since the close of the inspection of your facility on March 23, 2017, we note that you failed to submit your June 2017 product report, identifying product compounded in the previous six months.

Additionally, as explained above, the compounding of drug products using a bulk drug substance that appears on the 503B bulks list, or that appears on the drug shortage list is a condition of section 503B, which your firm failed to meet for a portion of the drug products you produced. Should you continue to compound and distribute drug products that do not meet the conditions of section 503B, the compounding and distribution of your drugs would be subject to the new drug approval requirement, the requirement to label drug products with adequate directions for use, and the Drug Supply Chain Security Act requirements.

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 the violations. Please include an explanation of each step being taken to prevent the recurrence of the 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 (**546956**). 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 Ms. Mariza Jafary via email at Mariza.Jafary@fda.hhs.gov or by telephone at 949-608-2977 and reference unique identifier (**546956**)**.**

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] On June 9, 2016, FDA issued a final guidance titled, Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act. This guidance describes FDA's interim regulatory policy for outsourcing facilities registered under section 503B of the FDCA while the 503B bulks list is being developed. Specifically, the guidance sets out conditions under which FDA does not intend to take action against an outsourcing facility for compounding a drug product using a bulk drug substance that is not included on the 503B list and does not appear on the drug shortage list in effect under section 506E at the time of compounding, distribution, and dispensing until the substance is identified in a final rule as included or not included on the 503B bulks list. These conditions include that the substance may be eligible for inclusion on the 503B bulks list, was nominated with adequate support for FDA to evaluate it, and has not been identified by FDA as a substance that appears to present significant safety risks pending further evaluation. GHRP-2, GHRP-6, serotonin HCl, and testosterone cypionate were nominated for inclusion on the 503B bulks list, but have been identified as substances that were not nominated with adequate support for FDA to evaluate the substances. DMSO, DHEA, HCG, nandrolone, phosphatidylcholine, and sermorelin were not nominated for inclusion on the 503B bulks list, nor did they appear on the drug shortage list in effect under section 506E at the time of compounding and distribution. For additional information, see the guidance at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469122.pdf

[4] The specific products made by your firm are drugs within the meaning of section 201(g) of the Act, [21 U.S.C. § 321(g)] because they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases and/or because they are intended to affect the structure or any function of the body. Further, they are "new drugs" within the meaning of section 201(p) of the FDCA [21 U.S.C. § 321(p)] because they are not generally recognized as safe and effective for their labeled uses.

[5] 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).