Auro Pharmacies Inc 9/24/18

Division of Pharmaceutical Quality Operations IV
19701 Fairchild, Irvine CA 92612-2506
Telephone: 949-608-2900
Fax: 949-608-4417

WARNING LETTER

VIA SIGNATURE CONFIRMED DELIVERY

September 24, 2018

Nayan Patel
President and Pharmacist-in-Charge
Auro Pharmacies, Inc.
511 S. Harbor Blvd, Suite F
La Habra, CA 90631-9375

Dear Mr. Patel:

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 September 1, 2016, and re-registered on October 12, 2016. From June 13, 2017, to June 29, 2017, an FDA investigator inspected your facility, Auro Pharmacies, Inc., 511 S. Harbor Blvd, Suite F, La Habra, CA 90631-9375. 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 June 29, 2017. FDA acknowledges receipt of your facility's responses, dated July 20, 2017, July 24, 2017, and August 2, 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, 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, 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, the FDA investigator noted that drug products produced by your facility failed to meet the conditions of section 503B. For example, the investigator noted:

1. Your facility compounded drug products using bulk drug substances including, but not limited to: Zinc Chloride, Selenium, and L-Carnitine. Drug products compounded using the aforementioned bulk drug substances are not eligible for the exemptions provided by section 503B, because the aforementioned bulk drug substances 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. Your facility failed to submit an initial product report to FDA in September 2016 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 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 observed that your firm produced drug products intended to be sterile in ISO-5 hoods that were not tested and certified under dynamic conditions.

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 establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).
3. 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).
4. Your firm does not have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release (21 CFR 211.165(a)).
5. 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)).
6. Your firm failed to clean and, where indicated by the nature of the drug, sterilize and process container closures to remove pyrogenic properties to assure that they are suitable for their intended use (21 CFR 211.94(c)).
7. 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 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.

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) of the FDCA [21 U.S.C. §§ 355(a) and 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. Further, 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

As noted above, your facility failed to submit a report to FDA upon initial registration as an outsourcing facility in September 2016, 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 are unable to fully evaluate the following corrective actions due to lack of adequate supporting documentation:

1. In your response dated July 20, 2017, you committed to recertify your hoods and cleanrooms under dynamic conditions. However, you did not provide any supporting documentation, such as recertification reports.
2. In your response dated July 20, 2017, you stated that your environmental monitoring sampling locations were chosen based on a validation study "*Performance Qualification for the Environmental Monitoring Program of the Sterile Compounding Cleanrooms*." You provided an addendum report of this study showing that you identified all microbes recovered in the cleanroom and the hoods. However, you did not provide the complete validation reports to justify the sampling locations. Furthermore, we noted that your revised SOP entitled "*Viable Air Particulates Monitoring*" instructs for a **(b)(4)** incubation of environmental sampling plates. However, you did not provide scientific justification for this limited incubation time.
3. In your responses dated July 20, 2017, and August 2, 2017, you committed to perform investigations into previous excursions resulting from your newly established limits. However, you did not provide documentation to demonstrate that all excursions were investigated. Furthermore, in one of your investigations you justified release of two lots of finished drug product with environmental monitoring excursions due to the lots passing

sterility and endotoxin testing. However, finished product testing, such as sterility and endotoxin testing, is not designed to justify product release with environmental excursions and your investigations should include a more robust analysis. In addition, you **(b)(4)** your alert and action limits and provided revised forms for documenting environmental results. However, your alert and action level for ISO 7 surface monitoring appears to be **(b)(4)** than industry standard and you did not provide justification for these set limits.

4. In regard to your sterility testing observation, you stated in your response dated July 20, 2017, that sterility testing is performed per the guidelines specified in USP <71> and provided your SOP titled "*Sterility Testing Using the* **(b)(4)**." However, your response did not include documentation to demonstrate that method suitability testing has been performed for each sterile drug product formulation you produce.

5. In your response dated July 20, 2017, you address our vial washing observation stating that you restricted access to the washing room and established a gowning requirement. You also provided a description of the interim washing method. However, you did not provide documentation to demonstrate that the stopper depyrogenation process has been validated. Furthermore, you did not provide documentation to demonstrate adequate controls are in place to prevent contamination during the transfer of washed vials and stoppers into the cleanroom.

6. In your response dated July 20, 2017, you address our stability observation stating that you had been using six months Beyond Use Dates (BUDs) at your 503A facility since 2012 and that "any extension of the shelf life beyond this date would require stability data." However, you did not provide supporting documentation, such as stability study reports to support the BUDs for all of your finished drug products. Your current practice of using BUDs established at your 503A facility without supporting documentation is not acceptable.

The following corrective action appears to be deficient:

Your firm did not validate the test methods used to determine your drug product strength. You also had numerous potency out-of-specification results at the time of inspection. You committed to complete an assay validation study for testing the strength of Methylcobalamin. However, you did not provide the validation report. In addition, it is unclear if you will validate the assay method used for all other finished drug products produced at your facility. Furthermore, your validation report for the **(b)(4)** particulate counter does not appear to have acceptance criteria for the spike recovery or the comparison between results generated at your facility and at your contract laboratory.

In addition, regarding observations related to the conditions of section 503B of the FDCA, your corrective actions appear adequate:

1. You state that you are no longer compounding products using bulk drug substances which do not appear in Category 1 of the FDA 503B bulks list or on the FDA shortages list.

2. You have submitted biannual product reports since December 2016.

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).

FDA strongly recommends 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 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 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 **565110**. 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, Compliance Officer via email at **Mariza.Jafary@fda.hhs.gov (mailto:Mariza.Jafary@fda.hhs.gov)** or by telephone at 949-608-2977 and reference unique identifier 565110**.**

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

---

[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. Bulk drug substances Zinc Chloride, Selenium, and L-Carnitine were nominated for inclusion on the 503B bulks list. They were not nominated with adequate support for FDA to evaluate the substance. For additional information, see the guidance at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469122.pdf (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).

More in Warning Letters (/ICECI/EnforcementActions/WarningLetters/default.htm)