California Pharmacy & Compounding Center 6/17/15

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Los Angeles District
19701 Fairchild
Irvine, CA 92612-2506

Telephone: 949-608-2900
Facsimile: 949-608-4417

WARNING LETTER

VIA UNITED PARCEL SERVICE
SIGNATURE REQUIRED

June 17, 2015

WL# 23-15

Glen A. Olsheim, Chief Financial Officer
California Pharmacy & Compounding Center
400 Birch Street, Suite 120
Newport Beach, CA 92660-2258

Dear Mr. Olsheim:

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 April 30, 2014, and again on November 24, 2014. From August 18, 2014, to August 25, 2014, and from October 14, 2014, to October 17, 2014, FDA investigators inspected your facility, California Pharmacy & Compounding Center, located at 400 Birch Street, Suite 120, Newport Beach, CA 92660-2258. During the inspections, the investigators observed serious deficiencies in your practices for producing sterile drug products, which put patients at risk. For example, the investigators observed that you did not monitor the pressure differential between your ISO 7 cleanroom and ISO 8 anteroom. Furthermore, the investigators noted that sterile production occurred from January 26, 2014, to March 19, 2014, and from March 21, 2014, to June 19, 2014, but your firm did not conduct any environmental monitoring during those periods of production. Therefore, your products may have been produced in an environment that poses a significant contamination risk. In addition, the investigators observed that you failed to meet the conditions under section 503B of the FDCA necessary for drugs produced by an outsourcing facility to qualify for exemptions from certain requirements under the FDCA. FDA issued a Form FDA 483 to your facility on August 25, 2014, and a second Form FDA 483 on October 17, 2014. FDA acknowledges receipt of your facility's responses, dated September 16, 2014 and November 6, 2014.

Based on these inspections, it appears your facility is producing drugs that violate the FDCA.

A. Compounded Drugs 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), 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 can 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)(l)] 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.

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 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.

B. Violations of the FDCA

The investigators noted that drug products that were intended or expected to be sterile were prepared, packed, or held under insanitary conditions whereby they may have been contaminated with filth or rendered injurious to health, causing them to be adulterated within the meaning of section 501(a)(2)(A) of the FDCA. Furthermore, FDA investigators observed significant CGMP violations at your facility, causing your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA.

In addition, FDA investigators observed that your facility failed to meet the conditions of section 503B of the FDCA. For example, during the inspections, the investigators observed that:

1. Some of your facility's drug product labels do not include the name, address, and phone number of your facility; dosage form and strength; a statement of quantity or volume, as appropriate; the date the drug was compounded; expiration date; and storage and handling instructions.
2. Some of your drug product labels do not include the statements, "This is a compounded drug" and "Not for Resale," and the labels of the drugs that you dispense or distribute other than pursuant to a prescription for an individual identified patient do not include the statement "Office Use Only."
3. Some of the container labels of your drug products do not include the following information to facilitate adverse event reporting: www.fda.gov/medwatch and 1-800-FDA-1088.

Because your compounded drug products have not met all of the conditions in section 503B of the FDCA, they are not eligible for the exemptions under section 503B from the FDA approval requirements in 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. [2]

Specific violations are described below.

Adulterated Drug Products

FDA investigators noted that drug products compounded in your facility that were 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 observed that you did not monitor the pressure differential between your ISO 7 cleanroom and ISO 8 anteroom. Furthermore, the investigators noted that sterile production occurred from January, 26 2014, to March 19, 2014, and from March 21, 2014, to June 19, 2014, but your firm did not conduct any environmental monitoring during those periods of production. Therefore, your products may have been produced in an environment that poses a significant contamination risk.

FDA investigators also noted CGMP violations at your facility, causing your drug products 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 ensure that manufacturing personnel wear clothing appropriate to protect drug product from contamination [21 CFR 211.28(a)].

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 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].

5. Your firm failed to establish an adequate system for maintaining equipment used to control the aseptic conditions [21 CFR 211.42(c)(10)(vi)].

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 your drug products.[3] Under sections 301(d) and 505(a) of the FDCA [21 U.S.C. §§ 331(d) and 355(a)], a new drug may not be introduced 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.

Misbranded Drug Products

You compound drug products that are intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners; therefore adequate directions 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 , and they are not exempt from the requirements of section 502(f)(1) of the FDCA (see , e.g., 21 CFR § 201.115).

The introduction or delivery for introduction into interstate commerce of these products therefore violates sections 301(a) of the FDCA. 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.

C. Corrective Actions

In your September 16, 2014, and November 6, 2014, responses to the Form FDA 483 inspectional observations, you described certain corrective actions taken in response to the observations. Although several of your proposed corrective actions appear adequate, others are deficient. For example, in response to our observation regarding inadequate environmental monitoring, you indicated that you have revised your environmental monitoring procedure and described an increased environmental monitoring sampling plan. However, during a follow-up inspection from October 14, 2014, to October 17, 2014, our investigators observed that your firm had not taken appropriate action when environmental monitoring results were outside of your defined specifications.

In your response to our observation of operators compounding sterile drug products with exposed skin and non-sterile garb, you indicated that this issue would be corrected by September 24, 2014. However, during a follow-up inspection from October 14, 2014, to October 17, 2014, our investigators noted that operators wore non-sterile goggles and a portion of their neck region was left exposed during the production of sterile products. In addition, you did not provide any documentation to demonstrate that you have successfully completed the corrective actions, such as developing adequate gowning procedures.

In your response to our observation of inadequate pressure differential monitoring, you indicated that this issue would be corrected by September 21, 2014. However, during a follow-up inspection from October 14, 2014, to October 17, 2014, our investigators observed that this issue had not been corrected.

In your response to our observation of inadequate media fill simulations, you indicated that your media fill test procedure has been modified to more accurately mimic your "most risky" compounding procedure. However, your response is inadequate as you are not simulating each type of container closure system (e.g., eye drop container) during media fill studies.

FDA strongly recommends that your management immediately undertake a comprehensive assessment of your operations, including facility design, procedures, personnel, processes, materials, and systems. In particular, this review should assess your aseptic processing operations. A third party consultant with relevant sterile drug manufacturing expertise could be useful in conducting this comprehensive evaluation. You should fully implement necessary corrections in order to ensure that the drug product(s) produced by your firm conform to the basic quality standards that ensure safety, identity, strength, quality, and purity.

D. 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. FDA intends to re-inspect your facility to verify corrective actions have been completed.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps 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 the corrective actions cannot be completed within fifteen working days, state the reason for the delay and the time frame within which the corrections will be completed. Your written notification should refer to the Warning Letter# 23-15, FEI: 3004600090.

Please address your reply to William Vitale, Compliance Officer, at the address above.

If you have questions regarding the contents of this letter, please contact William Vitale, at 949-608-2919.

Sincerely,
/S/
Alonza E. Cruse
Los Angeles District

Cc:
Virginia Herold, Executive Officer
California State Board of Pharmacy
1625 N. Market Boulevard, Suite N-219 Sacramento, CA 95834

David M. Mazzera, Ph.D.
Chief, Food and Drug Branch
California Department of Public Health
1500 Capitol Avenue, MS-7602
Sacramento, California

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1 See Pub. L. No. 113-54, § 102(a), 127 Stat. 587, 587-588 (2013).
2 See, e.g., section 503B(a)(11) of the FDCA [21 U.S.C. § 353b(a)(11)].