Inspections, Compliance, Enforcement, and Criminal Investigations

Zions Rx Formulations Services LLC dba Rx Formuations Serv. 8/15/14

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Los Angeles District
Pacific Region
19701 Fairchild
Irvine, CA 92612-2506
Telephone: 949-608-2900
FAX: 949-608-4415

WARNING LETTER

VIA UNITED PARCEL SERVICE
SIGNATURE REQUIRED

August 15, 2014

WL# 32-14

Troy A. Albright, Owner
Zion Rx Formulations Services, LLC
5949 E. University Drive
Mesa, AZ, 85205-7435

Dear Mr. Albright:
From December 3, 2013, to January 9, 2014, U.S. Food and Drug Administration (FDA) investigators conducted an inspection of your facility, Zion Rx Formulations Services ("Rx Formulations") located at 5949 E. University Drive, Mesa, Arizona 85205-7435. During the inspection, the investigators noted that you were not receiving valid prescriptions for individually identified patients for a portion of drug products you were producing. In addition, the investigators observed serious deficiencies in your practices for producing sterile drug products, which put patients at risk.

For example, *Nocardia,* sp. was identified in Rx Formulations' calcium gluconate 10% injection, lot #117466@8 by FDA and the Centers for Disease Control and Prevention, while investigating a complaint associated with your compounded calcium gluconate 10% injection. FDA also tested and confirmed that environmental samples collected in your facility tested positive for numerous gram-negative bacteria and spore-forming microbes, including fungi. During the inspection, the investigators observed operators processing sterile drug products with exposed skin on their faces. Additionally, your firm does not use sporicidal agents to clean the production areas, only infrequently performs viable and non-viable monitoring, and does not monitor pressure differentials throughout the day, especially during periods of production. Furthermore, our investigators found that your firm failed to demonstrate through appropriate studies that your hoods are able to provide adequate protection of the ISO 5 areas in which sterile products are processed. Therefore, your products may be produced in an environment that poses a significant contamination risk. A Form FDA 483 was issued to your firm on January 9, 2014.

Furthermore, the deficiencies in the practices at your firm for producing sterile drug products resulted in a recall in December 2013 of all lots of calcium gluconate 10% injection produced at your facility, as well as all lots of drug products produced in the same hood as the contaminated calcium gluconate 10% injection. These products were produced from November 7 to 24, 2013. On December 24, 2013, you expanded your recall to include all sterile products within expiry, which added Vitamin B-12 injections produced by the firm since November 24, 2013 to the list of recalled products.

Based on this inspection, it appears that you are producing drugs that violate the Federal Food, Drug, and Cosmetic Act (FDCA).

A. Compounded Drugs Under the FDCA

Section 503A of the FDCA [21 U.S.C. § 353a], describes the conditions under which certain compounded

human drug products are entitled to exemption from three sections of the FDCA: compliance with current good manufacturing practices (CGMP), section 501(a)(2)(B) [21 U.S.C § 351(a)(2)(B)]; labeling with adequate directions for use, section 502(f)(1) [21 U.S.C. § 352(f)(1)]; and FDA approval prior to marketing, section 505 of the FDCA [21 U.S.C. § 355(a)]. Receipt of valid prescriptions for individually-identified patients is one of the conditions for the exemptions under section 503A of the FDCA.

During our inspection, investigators observed that your firm did not receive valid prescriptions for individually-identified patients for a portion of the drug products you produced. Accordingly, the drugs you compounded without valid prescriptions for individually-identified patients were not entitled to the exemptions in section 503A of the FDCA.[1]

In addition, we remind you that there are a number of other conditions that must be satisfied to qualify for the exemptions in section 503A of the FDCA.[2]

B. Violations of the FDCA

The drug products that you manufacture and distribute without valid prescriptions for individually-identified patients are misbranded drugs within the meaning of section 502(f)(1) and adulterated drugs within the meaning of section 501(b) of the FDCA. In addition, as discussed below, your calcium gluconate drug product was adulterated within the meaning of section 501(a)(1) of the FDCA and all sterile products you manufacture are adulterated within the meaning of section 501(a)(2)(A) of the FDCA. In addition, because you manufacture and distribute drugs without valid prescriptions for individually-identified patients, the manufacture of those drugs is also subject to FDA's CGMP regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations (CFR), Parts 210 and 211. FDA investigators also observed significant CGMP violations at your facility, causing such drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA.

Misbranded Drug Products

Because the drug products for which you had not obtained valid prescriptions for individually-identified patients were intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners, adequate directions cannot be written for them 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).

Adulteration Charges

Additionally, FDA investigators noted that your sterile drug products 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. During the inspection the investigators observed operators processing sterile drug products with exposed skin on their faces. Additionally, your firm does not use sporicidal agents to clean the production areas, only infrequently performs viable and non-viable monitoring, and does not monitor pressure differentials throughout the day, especially during periods of production. Furthermore, our investigators found that your firm failed to demonstrate through appropriate studies that your hoods are able to provide adequate protection of the ISO 5 areas in which sterile products are processed. Therefore, your products may be produced in an environment that poses a significant contamination risk.

In addition, FDA and the Centers for Disease Control and Prevention identified *Nocardia*, sp. in calcium gluconate 10% injection, lot #117466@8. FDA also tested and confirmed that environmental samples collected in your facility tested positive for numerous gram-negative bacteria and spore-forming microbes, including fungi. These findings demonstrate that these drug products are adulterated within the meaning of section 501(a)(1) of the FDCA, in that it consists in whole or in part of any filthy, putrid, or decomposed substance. Furthermore, the contaminated calcium gluconate injection drug product that you produced is required to be sterile under the applicable USP monograph, and is therefore adulterated within the meaning of section 501(b) of the FDCA [21 U.S.C. 351(b)], in that the product did not meet USP compendia standards for quality and purity for sterility set forth in the USP General Chapter <1> for Injections.

FDA investigators also noted CGMP violations at your facility, causing the drug products for which you have not obtained valid prescriptions for individually-identified patients to be adulterated under section 501(a)(2)(B) of the FDCA. The violations include, for example:

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

2. 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)).

3. 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)).

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

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)).

6. 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)).

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 of the components used to make the drug and results in the drug being adulterated.

C. Corrective Actions

We acknowledge your action on December 12, 2013, to recall all lots of calcium gluconate 10% injection produced from November 7 to 24, 2013, at your facility and on December 24, 2013, to extend the recall to all sterile products within expiry, which added Vitamin B-12 injections, produced by the firm since November 24, 2013, to the list of recalled products.

You must correct all insanitary conditions at your firm. FDA strongly recommends 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.

In your January 28, 2014 response to the Form FDA 483, Inspectional Observations, issued at the close of the inspection, you stated that you intend to comply with United States Pharmacopeia (USP)-National Formulary (NF) General Chapter <797> Pharmaceutical Compounding--Sterile Preparations. However, as discussed above, because you were not getting prescriptions for a portion of the drug products you produce, your firm has manufactured and distributed drugs without valid prescriptions for individually-identified patients. The manufacture of such drugs is subject to FDA's drug CGMP regulations, 21 CFR Parts 210 and 211 and compliance with USP Chapter <797> is not sufficient to meet 210 and 211 requirements. Your firm's planned corrections do not meet the minimum requirements of 21 CFR Part 211, and there is no assurance that such human drug product(s) produced by your firm conform to the basic quality standards that ensure safety, identity, strength, quality, and purity.

In addition, in a letter dated December 19, 2013, you agreed that you would no longer produce non-patient specific orders for sterile drug products, but you do not state your intention with regard to obtaining prescriptions for compounded non-sterile products. You should be aware that prescriptions for individually identified patients are necessary for both sterile and non-sterile drug products to qualify for the exemptions in section 503A of the FD&C Act. As discussed above, your firm has manufactured and distributed drugs without valid prescriptions for individually identified patients, and therefore, any continued manufacturing of such drugs would subject them to FDA's drug CGMP regulations (21 CFR Parts 210 and 211). Therefore, you should fully implement corrections that meet the minimum requirements of 21 CFR Part 211 to provide assurance that the drug products produced by your firm conform to the basic quality standards that ensure safety, identity, strength, quality, and purity.

In addition, you should correct the violations of FDCA section 502(f)(1) noted above.

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 and FDA regulations.

We also request that you provide a detailed account of all steps you have taken to ensure that you will have no recurrent contamination in your cleanroom, and submit relevant procedures (e.g., cleaning and sanitization, and environmental monitoring (e.g., surface, personnel, and air)), sampling results, and trending.

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. Because at least one of your products was actually contaminated, and we observed insanitary conditions at your facility, if you have not already corrected the insanitary conditions at your firm, you should cease sterile operations pending completion of all necessary corrective actions.

Within fifteen working days of receipt of this letter, please notify this office in writing if you have taken any specific steps to correct violations and/or cease ongoing sterile production. 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 implemented. Your notification should be addressed to:

Nancy Schmidt, Acting Director
Compliance Branch
Los Angeles District
U.S. Food and Drug Administration
19701 Fairchild
Irvine, CA 92612-2506

If you have any questions regarding this letter, please contact David Whitman, Compliance Officer at 619-941-3769.

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

cc:

Hal Wand, Executive Director
Arizona Board of Pharmacy
1616 W. Adams St., Suite 120
Phoenix, AZ 85007

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[1]The Compounding Quality Act (CQA) contains a number of other provisions, including new exemptions and requirements for compounders seeking to operate as outsourcing facilities. A discussion of the CQA and the agency's plans to implement the new law may be found at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm[1].
[2] For example, section 503A also addresses anticipatory compounding, which includes compounding (not distribution) before receipt of a valid prescription order for an individual patient. We are not addressing anticipatory compounding here.

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Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

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1. /Drugs/default.htm