Ionia Pharmacy 12/22/15

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

W/L# 13-16

December 22, 2015

Curtis M. Boxley, Pharm.D., Pharmacist-in-Charge
Ionia Pharmacy, LLC
15421 Red Hill Avenue
Suite A
Tustin, CA 92780-7309

Dear Mr. Boxley:

Between March 3, 2015 and March 6, 2015, U.S. Food and Drug Administration (FDA) investigators conducted an inspection of your facility, Ionia Pharmacy, LLC, located at 15421 Red Hill Avenue, Suite A, Tustin, CA 92780-7309. This inspection was conducted after receipt of a MedWatch Report describing an adverse event associated with drug products prepared by your firm.

During the inspection, the investigators noted that you were not receiving valid prescriptions for individually-identified patients for a portion of the 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, the investigators noted that your firm's environmental sampling is conducted **(b)(4)**, which can cause a false impression of the effectiveness of your firm's cleaning and sanitation program. Also, your firm does not monitor pressure differentials between the ISO 5 hood and the ISO 7 cleanroom. In addition, non-sterile wipes are used to disinfect the ISO 5 area, and items introduced to the ISO 5 hood from the ISO 7 area are not always disinfected appropriately (for example, **(b)(4)** vials). Moreover, non-sterile **(b)(4)** is used to **(b)(4)**. The investigators also observed operators with facial skin and eyes exposed while working in the ISO 5 and ISO 7 areas. Furthermore, your firm failed to demonstrate through appropriate studies that the hoods are able to provide adequate protection of the ISO 5 area in which sterile products are being produced. Therefore, your products may be produced in an environment that poses a significant contamination risk.

FDA issued a Form FDA 483 to your firm on March 6, 2015, and subsequently issued an amended Form FDA 483 on March 18, 2015. FDA acknowledges receipt of your firm's response to the Form FDA 483, dated March 27, 2015.

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

During the FDA inspection, the investigators observed that your firm does not receive valid prescriptions for individually-identified patients for a portion of the drug products you produce. Accordingly, the drugs you compound without valid prescriptions for individually identified patients are not entitled to the exemptions in section 503A.

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.***1***

B. Violations of the FDCA

Because the drug products that you manufacture and distribute without valid prescriptions for individually-identified patients are not the subject of approved applications, they are unapproved new drugs and misbranded drugs in violation of sections 505(a) and 502(±)(1) of the FDCA, respectively. In addition, drug products that are 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 [21 U.S.C. § 351(a)(2)(A)]. Furthermore, because you manufacture and distribute a portion of your drugs without valid prescription for individually-identified patients, the manufacture of those drugs is subject to FDA's CGMP regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations (CFR), Parts 210 and 211. 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 [21 U.S.C. § 351(a)(2)(B)].

Unapproved New Drug Products

You do not have any FDA-approved applications on file for the drug products for which you have not obtained valid prescriptions for individually-identified patients***2***. Under sections 505(a) and 301(d) 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. Your marketing of these products, or other applicable products, without an approved application violates these provisions of the FDCA.

Misbranded Drug Products

Because the drug products for which you have not obtained valid prescriptions for individually-identified patients are 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].

Under section 301(a) of the FDCA the introduction or delivery for introduction into interstate commerce of any drug that is misbranded 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 of the components used to make the drug and results in the drug being misbranded.

Adulteration Charges

Additionally, the FDA investigators observed that drug products in your facility 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 investigator observed serious deficiencies in your practices for producing sterile drug products, which put patients at risk. For Example, the investigators noted that your firm's environmental sampling is conducted **(b)(4)**, which can cause a false impression of the effectiveness of your firm's cleaning and sanitation program. Also, your firm does not monitor pressure differentials between the ISO 5 hood and the ISO 7 cleanroom. In addition, non-sterile wipes are used to disinfect the ISO 5 area, and items introduced to the ISO 5 hood from the ISO 7 area are not always disinfected appropriately (for example, **(b)(4)** vials). Moreover, non-sterile **(b)(4)** is used to **(b)(4)**. The investigators also observed operators with facial skin and eyes exposed while working in the ISO 5 and ISO 7 areas. Furthermore, your firm failed to demonstrate through appropriate studies that the hoods are able to provide adequate protection of the ISO 5 area in which sterile products are being produced. Therefore, your products may be produced in an environment that poses a significant contamination risk.

The FDA investigators also observed 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 failed to ensure the system for cleaning and disinfecting equipment is adequate to produce aseptic conditions. (21 CFR 211.42(c)(10)(v))
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 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 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))

7. Your firm does not have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product prior to release. (21 CFR 211.165(a))

Under section 301(a) of the FDCA the introduction or delivery for introduction into interstate commerce of any drug that is adulterated is a prohibited act. Further, 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 of the components used to make the drug and results in the drug being adulterated.

C. Corrective Actions

We acknowledge receipt of your response to the Form FDA 483, dated March 27, 2015, in which you state your firm is "in the process of closing the business." However, to date, we have not received confirmation that your firm has ceased operations.

To the extent that your firm remains operational, or should your firm resume operations in the future, before resuming production of sterile drugs, FDA strongly recommends that management first 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. Please be aware that section 501(a)(2)(A) of the FDCA concerning insanitary conditions applies regardless of whether the drugs are compounded and distributed after receipt of a prescription for an identified individual patient. In addition, should you continue to manufacture and distribute drug products without valid prescriptions for individually-identified patients, the manufacture of such drugs would be subject to FDA's drug CGMP regulations (21 CFR Parts 210 and 211), among other requirements described above, and, before doing so, you should fully implement corrections that meet the minimum requirements of 21 CFR Part 211 in order 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 your response to the Form FDA 483 dated March 27, 2015, you referenced your purported compliance with the United States Pharmacopeia (USP)-National Formulary (NF) General Chapter <797> Pharmaceutical Compounding--Sterile Preparations. As noted above your firm has manufactured and distributed drugs without valid prescriptions for individually-identified patients, and the manufacture of such drugs is subject to FDA's drug CGMP regulations, 21 CFR parts 210 and 211.

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, as amended by the Food and Drug Administration Safety and Innovation Act (Pub.L. 112-144, Title VII, section 711). We note that you have chosen to hire a contract testing laboratory to perform some of the required testing of your finished drug products. 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 your compounded drug products are neither adulterated nor misbranded. See 21 CFR 210.1 (b), 21 CFR 200.10(b).

In addition, you should also correct the violations of sections 501(a)(2)(A) and 502(f)(1) of the FDCA, 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 fi1m complies with all requirements of federal law and 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. Your written notification should be addressed to:

CAPT Daniel Cline, Acting Director, Compliance Branch
FDA Los Angeles District Office
U.S. Food and Drug Administration
19701 Fairchild
Irvine, CA 92612

If you have questions regarding any issues in this letter, please contact Dr. Brullo via email at Raymond.Brullo@fda.hhs.gov or by phone at 949-608-2918.

Sincerely,
/S/
LCDR Steven Porter
Acting District Director
Los Angeles District

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

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1 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.

2 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) [21 U.S.C. 321(p)] of the FDCA because they are not generally recognized as safe and effective for their labeled uses.

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