Inspections, Compliance, Enforcement, and Criminal Investigations

Pharmacy Creations 6/23/14

Department of Health and Human Services

Public Health Service
Food and Drug Administration
New Jersey District Office
Central Region
Waterview Corporate Center
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Parsippany, New Jersey 07054
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WARNING LETTER

June 23, 2014

VIA UNITED PARCEL SERVICE

14-NWJ-09

Scott Karolchyk, R.Ph., MS, Pharmacist-in-Charge and Co-owner
Bernard Covalesky, R.Ph, Co-owner
Pharmacy Creations
540 Route 10 West
Randolph, NJ 07869

Dear Mr. Karolchyk and Mr. Covalesky:

From August 5, 2013 to August 19, 2013, U.S. Food and Drug Administration (FDA) investigators conducted an inspection of your facility, Pharmacy Creations, located at 540 Route 10 West, Randolph, NJ 07869. 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. It was also noted that your firm continues to make domperidone drug products, despite having received prior warnings regarding this practice in a Warning Letter issued on October 31, 2006, and in a meeting with FDA on June 11, 2008. Domperidone is not the subject of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, nor is it a component of an FDA-approved human drug product, nor does it appear on a list developed by the Secretary under section 503A(b)(1)(A)(i)(III) of the Federal Food Drug, and Cosmetic Act (FDCA) [21 U.S.C.§353a]. In addition, the investigators observed serious deficiencies in your practices for producing sterile drug products, which put patients at risk. For example, your firm produces sterile injectable drug products in multiple-dose containers without a preservative added to the formulations. There is a significant risk that your formulation is unsuitable formultiple uses, and will present an increased risk of infection to patients. In addition, your firm produces lyophilized epinephrine **(b)(4)**. Your firm has failed to demonstrate that the process does not place product at risk of microbial contamination and is capable of producing product of a consistent potency. These observations and others were noted on a Form FDA 483, issued on August 19, 2013.

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**

At the time FDA inspected your facility, there were conflicting judicial decisions regarding the applicability of section 503A of the FDCA [21 U.S.C. § 353a], which *exempts* compounded drugs from several key statutory requirements if certain conditions are met.***1*** Nevertheless, receipt of valid prescriptions for individually-identified patients prior to distribution of compounded drugs was relevant for both section 503A of the FDCA and the agency's Compliance Policy Guide 460.200 on Pharmacy Compounding (CPG) (2002), which was then in effect.***2*** During the FDA inspection, investigators observed that your firm does not receive valid prescriptions for individually-identified patients for a portion of the drug products you produce. Based on this factor alone, those drugs were not entitled to the statutory exemptions for compounded drugs described in section 503A of the FDCA and did not qualify for the agency's exercise of enforcement discretion set forth in the CPG.***3***

In addition, under the CPG, when determining whether to initiate enforcement action, FDA considered whether a firm compounded finished drugs from bulk active ingredients that were not components of FDA-approved drugs without an

FDA sanctioned investigational new drug application. Because domperidone was not a component of an FDA-approved human drug, your compounded drugs containing domperidone would not qualify for the exercise of enforcement discretion set forth in the CPG. Further, the exemptions provided by section 503A(a) did not apply to compounded drug products containing domperidone because domperidone was not the subject of an applicable USP or NF monograph, was not a component of an FDA-approved human drug under section 503A(b)(1)(A)(i) of the FDCA, and did not appear on a list developed by the Secretary under 503A(b)(1)(A)(i)(III).

Since FDA inspected your facility, Congress enacted and the President signed into law the Compounding Quality Act (CQA)***4***, which amended FDCA section 503A by eliminating the advertising restrictions that had been the basis for conflicting judicial decisions. The CQA otherwise left section 503A intact, and so clarified that the remainder of section 503A is applicable in every federal judicial circuit, including the requirement for valid prescriptions for individually identified patients, and the requirement to only compound drug products using bulk drug substances if each bulk drug substance is the subject of an applicable USP or NF monograph, is a component of an FDA-approved human drug, or appears on a list developed by the Secretary under section 503A(b)(l)(A)(i)(III). Accordingly, the drugs you compound without valid prescriptions for individually-identified patients and any drug products you compound using domperidone, which is not the subject of an applicable USP or NF monograph, not a component of an FDA-approved human drug, and did not appear on a list developed by the Secretary under section 503A(b)(1)(A)(i)(III), are not entitled to the exemptions in section 503A.***5***

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.***6***

B. Violations of the FDCA

Because both the domperidone drug products and 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(f)(1) [21 U.S.C. *§* 355(a) and 352(f)(1)] of the FDCA, respectively.

In addition, the manufacture of those drug products is also subject to FDA's Current Good Manufacturing Practice (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 such drug product(s) 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.***7*** Additionally, you produce domperidone drug products that are not the subject of an applicable USP or NF monograph, are not a component of an FDA-approved drug under section 503A (b)(1)(A)(i) of the FDCA, and do not appear on a list developed by the Secretary under 503A(b)(1)(A)(i)(III).***7*** 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 into or delivered for introduction into interstate commerce unless an application approved by FDA under section 505 of the FDCA [21 U.S.C. § 355) 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 domperidone drug products and 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 [21 U.S.C. § 352(f)(1)], 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 [21 U.S.C. §331(a)]. It is also 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

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 [21 U.S.C. § 351(a)(2)(B)]. The violations include, for example:

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

2. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(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 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)).

5. 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 they are suitable for their intended use (21 CFR 211.94(c)).

6. Your firm failed to test samples of each component for conformity with all appropriate written specifications for purity, strength, and quality (21 CFR 211.84(d)(2)) and your firm failed to subject each lot of a component that is liable to microbiological contamination that is objectionable in view of its intended use to microbiological tests before use (21 CFR 211.84(d)(6)).

7. Your firm did not conduct, for each batch of drug product purporting to be sterile and/or pyrogen-free, appropriate laboratory testing to determine whether each batch was sterile or pyrogen-free (21 CFR 211.167 (a)).

8. Your firm did 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)).

Items 4, 6, 7, and 8 are based on repeat observations from the warning letter dated October 31, 2006.

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

C. Corrective Actions

In your response dated September 3, 2013, to the Form FDA-483, you reference your purported compliance with United States Pharmacopeia (USP)-National Formulary (NF) General Chapter <797> Pharmaceutical Compounding -- Sterile Preparations. However, as discussed above, your firm has manufactured and distributed drug products 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). Furthermore, on August 26, 2013, you recalled two lots of products as a result of sterility failures. 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 and design. A third party consultant with relevant sterile drug manufacturing expertise could be useful in conductingthis comprehensive evaluation. 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 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 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 contract testing laboratories to perform some of the required testing of your finished drug products. FDA inspected these laboratories in 2012 and 2013 and observed deficiencies in their practices. 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 introduce into interstate commerce 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 FDCA section 505(a) and 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.

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 within15 working days, state the reason for the delay and the time frame within which you will complete the correction. Your written notification should be addressed to:

Erin McCaffery, Compliance Officer
FDA New Jersey District Office
U.S. Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd, 3rd Floor
Parsippany, NJ 07054

If you have questions regarding any issues in this letter, please contact our office at 973-331-4993.

Sincerely,
/S/
Diana Amador Toro
District Director

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1 *Compare Western States Med. Ctr.* v. *Shalala,* 238 F.3d 1090 (9th Cir. 2001) *with Medical Ctr. Pharm.* v. *Mukasey,* 536 F.3d 383 (5th Cir. 2008).
2 The CPG set forth a non-exhaustive list of factors that FDA considered in determining whether to take enforcement action when the scope and nature of a pharmacy's activities raised concerns. This CPG has been withdrawn in light of new legislation. See below.
3 *See* 21 U.S.C. § 353a(a) (granting compounded drugs statutoryexemptionsif, among other things,"the drug product is compounded for an identified individual patient based on the...receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient...."); CPG at 2 ("FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of human drugs upon receipt of a valid prescription for an individually-identified patient from a licensed practitioner. This traditional activity is not the subject of this guidance.").
4 Drug Quality and Security Act, Public Law 113-54, 127 Stat. 587 (Nov. 27, 2013).
5 The 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]
6 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.
7 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. 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.

Links on this page:

1. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding!default.htm