The Apothecary Shoppe LLC 8/19/16

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Dallas District Office
4040 North Central Expressway
Suite 300
Dallas, Texas 75204-3128

August 19, 2016

2016-DAL-WL-33

WARNING LETTER

VIA UPS Express

Thomas Marti, President
CFP Acquisitions, Inc.
dba The Apothecary Shoppe
2530 N Elm Place
Broken Arrow, Oklahoma 74012

Dear Mr. Marti:

From March 3, 2015, to March 13, 2015, U.S. Food and Drug Administration (FDA) Investigators conducted an inspection of your facility, The Apothecary Shoppe, located at 6136 E 51st St., Tulsa, Oklahoma. During the inspection, the investigators noted that your firm was not receiving valid prescriptions for individually-identified patients for a portion of the drug products your firm was producing. The investigators also noted that your firm produces domperidone products. 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, and it does not 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(b)(1)(A)(i)(III)]. Furthermore, FDA investigators observed that your firm produced a drug product (potassium chloride) that appears on a list, published by the FDA at Title 21 Code of Federal Regulations (CFR) Part 216, of drugs that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective.

In addition, the FDA investigators observed serious deficiencies in your firm's practices for producing sterile drug products, which put patients at risk. For example, our investigators observed that the pressure differential between the ISO 8 room and the unclassified area measured zero. Also, your firm does not use sterile wipes or a sporicidal agent as part of the disinfection program for the ISO 5 laminar hoods and ISO 7 cleanroom where sterile drug products are prepared. Therefore, your firm's products may be produced in an environment that poses a significant contamination risk.

FDA issued a Form FDA 483, Inspectional Observations, to your firm on March 13, 2015. FDA acknowledges receipt of your firm's response to the Form FDA 483, faxed to Dallas District on April 3, 2015.

Based on this inspection, it appears that your firm is producing drugs that violate the FDCA.

A. Compounded Drugs under the FDCA

Section 503A of the FDCA describes the conditions under which certain compounded human drug products qualify for exemptions from three sections of the FDCA: compliance with current good manufacturing practice (CGMP) requirements, 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 of the FDCA. 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 your firm produces.

Another condition that must be met for a compounded drug to qualify for the exemptions under section 503A of the FDCA is that it is compounded using bulk drug substances that: (I) comply with the standards of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, if a monograph exists, and the USP chapter on pharmacy compounding; (II) if such a monograph does not exist, are components of drugs approved by the Secretary; or (III) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, that appear on a list developed by the Secretary through regulation (section 503A(b)(1)(A)(i)). Compounded drug products containing the bulk drug substance domperidone[1] are not eligible for the exemptions provided by subsection (a) of 503A because domperidone is not the subject of an applicable USP or NF monograph, not a component of an FDA-approved human drug, and does not appear on a list of bulk drug substances that may be used for compounding developed by the Secretary. [2]

Yet another condition that must be met for a compounded drug to qualify for the exemptions under section 503A of the FDCA is that the licensed pharmacist or licensed physician does not compound a drug product that appears on a list published by the FDA at Title 21 CFR Part 216 of drugs that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective ("withdrawn or removed list"). Investigators observed that your firm produced a drug product that appears on

the withdrawn or removed list at 21 CFR Part 216. Specifically, your firm produced potassium chloride 10 mEq capsule(s) (corn free), which is equivalent to approximately 750 mg potassium per capsule. The withdrawn or removed list includes “all solid oral dosage form drug products containing potassium chloride that supply 100 milligrams or more of potassium per dosage unit (except for controlled-release dosage forms and those products formulated for preparation of solution prior to ingestion).”

Accordingly, drugs that your firm compounds are not entitled to the exemptions in section 503A of the FDCA.

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.[3]

B. Violations of the FDCA

Because your firm compounded and distributed drug products without valid prescriptions for individually-identified patients, drug products containing domperidone, and drug products that appear on the withdrawn or removed list at 21 CFR Part 216, and because none of these drug products was the subject of approved applications, your firm was producing unapproved new drugs and misbranded drugs in violation of sections 505(a) and 502(f)(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 whereby they may have been 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 your firm manufactured and distributed drug products without valid prescriptions for individually-identified patients, drug products that contain the bulk drug substance domperidone, and drug products that appear on the withdrawn or removed list at 21 CFR Part 216, your firm is producing drug products that are 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 your firm’s 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, the domperidone drug products, or the drug products that appear on the withdrawn or removed list at 21 CFR Part 216. [4][5] 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

Your firm compounded drug products for which your firm has not obtained valid prescriptions for individually-identified patients, drug products in which your firm used the bulk drug substance domperidone, and drug products which appear on the withdrawn or removed list at 21 CFR Part 216. Because these drug products are intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners, adequate directions for use 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 requirement 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 such products therefore violates section 301(a) of the FDCA [21 U.S.C. § 331(a)]. Further, 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 and results in the drug being misbranded.

Adulterated Drug Products

Additionally, FDA investigators observed that drug products 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 [21 U.S.C. § 351(a)(2)(A)]. For example, our investigators observed that the pressure differential between the ISO 8 room and the unclassified area measured zero. Also, your firm does not use sterile wipes or a sporicidal agent as part of the disinfection program for the ISO 5 laminar hoods and ISO 7 cleanroom where sterile drug products are prepared. 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 your firm has not obtained valid prescriptions for individually-identified patients, the drug products containing the bulk drug substance domperidone, and the drug products that appear on the withdrawn or removed list at 21 CFR Part 216, to be adulterated under section 501(a)(2)(B) of the FDCA [21 U.S.C. § 351(a)(2)(B)]. The violations include, but are not limited to, the following:

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 establish an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions (21 CFR 211.42(c)(10)(v)).

4. 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)).

5. 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)).

6. Your firm failed to ensure manufacturing equipment is routinely calibrated, inspected or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained (21 CFR 211.68(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, 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 adulterated.

C. Corrective Actions

FDA acknowledges receipt of your firm's response to the Form FDA 483, faxed to the Dallas District on April 3, 2015, in which your firm described certain corrective actions it took in response to the Form FDA 483 observations and in which your firm stated that it "intend[] to compound products for identified individual patients based upon receipt of valid prescription order or notation in compliance with the provisions of 503A going forward." FDA also acknowledges your firm's statement during the investigation that it does not plan to **(b)(4)** and that it stopped making products containing the bulk drug substance domperidone. FDA reminds you that there are a number of other conditions that must be satisfied to qualify for the exemptions in section 503A of the FDCA and that it is your responsibility to ensure compliance with applicable provisions of the FDCA and regulations.

Although some of your corrective actions regarding insanitary conditions appear adequate, some of your responses cannot be fully evaluated by FDA because of insufficient supporting documentation. For example, you did not provide documentation to support that your laminar flow hood, ante room, and cleanroom were recertified.

FDA also acknowledges your firm's actions taken in response to requests from the Oklahoma Board of Pharmacy to recall all compounded sterile products produced from March 10, 2015, through May 20, 2015, within expiry, and to cease production of all sterile compounded drug products until notice was given by the Oklahoma Board of Pharmacy to resume sterile compounding on August 17, 2015.

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. FDA intends to verify the implementation and adequacy of your firm's corrective actions during FDA's next inspection

Please be aware that section 501(a)(2)(A) of the FDCA concerning insanitary conditions applies regardless of whether the conditions of section 503A are met. In addition, if you continue to manufacture and distribute drug products containing the bulk drug substance domperidone, drug products without valid prescriptions for individually-identified patients, or drug products listed at 21 CFR Part 216, 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 regarding safety, identity, strength, quality, and purity. Please note that corrective actions described in your firm's response to the Form FDA 483 to specific CGMP observations do not appear adequate. For example, your firm's response to the Form FDA 483 did not address validation of the sterilization process used by your firm.

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 may re-inspect to verify corrective actions have been completed.

Within 15 working days of receipt of this letter, please notify this office in writing if you have taken any specific steps 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 refer to the Warning Letter Number above (2016-DAL-WL-33). Please address your reply to John W. Diehl, Compliance Officer, at the address above.

If you have questions regarding the content of this letter, please contact Mr. Diehl at 214-253-5288.

Sincerely,
/S/
Amy Barringer
Acting Dallas District Director

CC:

Cindy Fain, D. Ph.
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[1] Domperidone was nominated for inclusion on the list of bulk drug substances that can be used in compounding that must be developed through regulation pursuant to section 503A(b)(1)(A)(i)(III) of the FD&C Act (503A bulks list). On June 9, 2016, FDA issued a final guidance titled, *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act*. This guidance describes FDA's regulatory policy for State-licensed pharmacies, Federal facilities, and licensed physicians that compound human drug products using bulk drug substances that do not otherwise meet the conditions of 503A(b)(1)(A)(i) while the 503A bulks list is being developed. Specifically, the guidance sets out the conditions under which FDA does not intend to take action against a State-licensed pharmacy, Federal facility, or licensed physician for compounding a drug product using a bulk drug substance that is not the subject of an applicable USP or NF monograph or a component of an FDA-approved drug, until the substance is identified in a final rule as included or not included on the 503A bulks list. These conditions include that the substance may be eligible for inclusion on the 503A bulks list, was nominated with sufficient supporting information 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. Domperidone has been identified as a substance that appears to present significant safety risks. For additional information, see the guidance at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469120.pdf.

[2]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.

[3] 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.