Cape Apothecary, Inc. 8/12/16

Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Baltimore District
6000 Metro Drive, Suite 101
Baltimore, MD 21215
Telephone: (410) 779-5455
FAX: (410) 779-5407

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER

August 12, 2016

Thomas Wilson, PharmD
Cape Apothecary, Inc.
1384 Cape Saint Claire Road
Annapolis, MD 21401

Dear Dr. Wilson:

From September 21, 2015, to October 7, 2015, U.S. Food and Drug Administration (FDA) investigators conducted an inspection of your facility, Cape Apothecary, Inc., located at 1384 Cape Saint Claire Rd, Annapolis, MD 21401. 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 and that you produce domperidone products. 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 did not use a sporicidal agent and used non-sterile sanitizers in the aseptic processing area. Additionally, operators were observed placing materials and components into the ISO 5 hood with their ungloved hand. Furthermore, your firm failed to demonstrate through appropriate studies that your hood is able to provide adequate protection of the ISO 5 area in which sterile products are processed. Therefore, your products may be produced in an environment that poses a significant contamination risk.

FDA investigators collected environmental samples of multiple locations in your facility, including the ISO 5 area. Testing results of these samples identified microbial contamination in multiple locations, including spore-forming bacteria within your ISO 5 hood.

A Form FDA 483 was issued to your firm on October 7, 2015. FDA acknowledges receipt of your facility's responses dated October 27, 2015, November 6, 2015, November 9, 2015, and April 8, 2016. We also acknowledge your action on November 5, 2015, to voluntarily recall all sterile drug products within expiry and to discontinue sterile production until adequate corrective actions have been implemented.

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 may 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 of the FDCA, Section 505 [21 U.S.C. § 355]. Receipt of valid prescriptions for individually identified patients is one of the conditions necessary to qualify 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.

Another condition that must be met for a compounded drug to qualify for the exemptions under section 503A is that it is compounded from 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 domperidone are not eligible for the exemptions under section 503A of the FDCA because domperidone is not the subject of an applicable USP or NF monograph, is not a component of an FDA-approved human drug, and does not appear on a list developed by the Secretary.***1***

Accordingly, the drugs you compound without valid prescriptions for individually-identified patients and any drug products you compound using domperidone are not entitled to the exemptions in section 503A.

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

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(f)(1) of the FDCA, respectively. Furthermore, the domperidone drug products that you produce are misbranded drugs in violation of Section 502(f)(1) of the FDCA.

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 you manufacture and distribute a portion of your drugs without valid prescriptions for individually-identified patients and manufacture and distribute drug products containing the bulk drug substance domperidone, the manufacture of such 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 observed significant CGMP violations relating to aseptic processing at your facility, causing drug products intended or expected to be sterile that were manufactured and distributed without a prescription to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA.

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.***3*** Under Sections 505(a) and 301(d) of the FDCA [21 USC §§ 355(a) and 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 domperidone drug products and 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].

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 misbranded.

Adulterated Drug Products

Additionally, the 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 the drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, the investigators noted that your firm did not use a sporicidal agent and used non-sterile sanitizers in the aseptic processing area. Additionally, operators were observed placing materials and components into the ISO 5 hood with their ungloved hand. Furthermore, your firm failed to demonstrate through appropriate studies that your hood is able to provide adequate protection of the ISO 5 area in which sterile products are processed. Therefore, your products may be produced in an environment that poses a significant contamination risk.

FDA investigators collected environmental samples of multiple locations in your facility, including the ISO 5 area Testing results of these samples identified microbial contamination in multiple locations, including spore-forming bacteria within your ISO 5 hood.

The FDA investigators also observed CGMP violations at your facility, causing the drug products in your facility intended or expected to be sterile 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 maintaining equipment used to control the aseptic conditions [21 CFR 211.42(c)(10)(vi)].

2. 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)].

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 establish 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 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)].

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

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

C. Corrective Actions

We acknowledge your action on November 5, 2015, to voluntarily recall all sterile drug products within expiry and to discontinue sterile production until adequate corrective actions have been implemented. We have reviewed your firm's corrective actions, as documented in your October 27, 2015, November 6, 2015, November 9, 2015, and April 8, 2016 responses. Although some of your proposed corrective actions appear adequate, others are deficient For example, while you have made improvements to your disinfection program, you have not demonstrated through environmental monitoring that your ISO 5 hood has been adequately cleaned and disinfected. Other deficiencies in your environmental monitoring program include lack of monitoring of the ISO 8 ante room. Additionally, your gowning procedure does not specifiy the use of sterile gloves and when gloves will be donned in the gowning sequence. Further, your glassware cleaning procedure does not provide sufficient detail on how endotoxins or pyrogens will be removed from the glassware used in the production of sterile drug products.

If you decide to resume production of sterile drugs, 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.

As discussed above, your firm has manufactured and distributed drugs without valid prescriptions for individually-identified patients, and your firm manufactures and distributes drug products containing the bulk drug substance domperidone, which is not permitted under section 503A. The manufacture of such drugs is subject to FDA's drug CGMP regulations (21 CFR 210 and 211). Before resuming such operations, 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 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 VJJ, section 711).

You should also correct the violations of FDCA sections 502(f)(1) and 505(a) 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, including FDA regulations.

If you decide to resume sterile operations, 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 if you have taken any specific steps to correct violations, or you may inform us that you do not intend to resume production of sterile drugs. If you intend to resume production of sterile drugs in the future, 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. In addition to taking appropriate corrective actions, you should notify this office 15 working days prior to resuming production of any sterile drugs in the future. Your written notification should be addressed to:

Ernest F. Bizjak, Compliance Officer
FDA Baltimore District Office
U.S. Food and Drug Administration
6000 Metro Drive, Suite 101
Baltimore, MD 21215

If you have questions regarding any issues in this letter, please contact Mr. Bizjak via email at emest.bizjak@fda.hhs.gov or by phone at 301-796-4081.

Sincerely,
/S/
Evelyn Bonnin
District Director
Baltimore District

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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)(I)(A)(i)(lll) of the FDCA (503A bulks list). See section 503A(b)(I)(A)(i)(III). 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)(l)(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 being 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 that it 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/GuidanceComplianceRegulatorylnformation/Guidances/UCM469120.pdf.

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.

3 The specific products made by your firm are drugs within the meaning of section 201(g) of the FDCA [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) of the FDCA [21 U.S.C. § 321(p)] because they are not generally recognized as safe and effective for their labeled uses.