Tri-Coast Pharmacy 8/20/18

August 20, 2018

CMS Case # 525312

WARNING LETTER

VIA UPS OVERNIGHT

Kevin P. O'Connell, Owner
Tri-Coast Pharmacy, Inc.
14125 US Highway 1
Juno Beach, FL 33408-1425

Mr. O'Connell:

From October 11, 2016, to October 21, 2016, U.S. Food and Drug Administration (FDA) investigators inspected your facility, Tri-Coast Pharmacy, Inc., located at 14125 US Highway 1, Juno Beach, FL 33408-1425. During the inspection, the investigators noted that drug products you produced failed to meet the conditions of section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA) [21 U.S.C. § 353a] for exemption from certain provisions of the FDCA. In addition, the investigators noted serious deficiencies in your practices for producing sterile drug products, which put patients at risk.

FDA issued a Form FDA 483 to your firm on October 21, 2016. FDA acknowledges receipt of your facility's responses, dated November 9, 2016, and January 4, 2017. FDA also acknowledges your voluntary recall, initiated on November 17, 2016, of all sterile drug products produced from May 17, 2016, to November 17, 2016, due to lack of sterility assurance. In addition, we acknowledge that you ceased sterile drug production on November 22, 2016 and resumed on December 8, 2016. Further, we acknowledge that following the April 17, 2017, Florida Department of Health (FLDOH) order of emergency suspension of your pharmacy permit, you relinquished your pharmacy permit on May 4, 2017, and your firm is no longer operational.

Based on this inspection, it appears that you produced drug products that violate the FDCA.

A. Compounded Drug Products Under the FDCA

Section 503A of the FDCA describes the conditions under which human drug products compounded by a licensed pharmacist in a State licensed pharmacy or a Federal facility, or a licensed physician, qualify for exemptions from three sections of the FDCA: compliance with current good manufacturing practice (CGMP) (section 501(a)(2)(B)); labeling with adequate directions for use (section 502(f)(1)); and FDA approval prior to marketing (section 505) [21 U.S.C. §§ 351(a)(2)(B), 352(f)(1) and 355(a)].[1] Receipt of valid prescriptions for individually-identified patients is one of the conditions for the exemptions under section 503A.

In addition, for a compounded drug product to qualify for the exemptions under section 503A, bulk drug substances used to compound it must: (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, be 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, appear on a list developed by the Secretary through regulation ("503A bulks list") (section 503A(b)(1)(A)(i) of the FDCA).

B. Failure to Meet the Conditions of Section 503A

During the inspection, the FDA investigators collected evidence indicating that drug products produced by your firm failed to meet the conditions of section 503A. For example, FDA noted that your firm compounded drug products using **(b)(4)**. Drug products compounded using **(b)(4)** are not eligible for the exemptions provided by section 503A(a) because these bulk drug substances are not the subjects of applicable USP or NF monographs, are not components of FDA-approved human drugs, and do not appear on the 503A bulks list.[2]

Therefore, you compounded drug products that do not meet the conditions of section 503A and are not eligible for the exemptions from the FDA approval requirement of section 505 of the FDCA, the requirement under section 502(f)(1) of the FDCA that labeling bear adequate directions for use, and the requirement of compliance with CGMP under section 501(a)(2)(B) of the FDCA. In the remainder of this letter, we refer to your drug products that do not qualify for exemptions under section 503A as the "ineligible drug products."

Specific violations are described below.

C. Violations of the FDCA

Adulterated Drug Products

The FDA investigators noted that drug products 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:

1. The **(b)(4)** located in the laminar flow ISO 5 hoods (Hood **(b)(4)** and **(b)(4)**) contain significant brown stains.
2. Your firm transferred partially **(b)(4)** from an ISO 5 classified laminar **(b)(4)** the **(b)(4)** in another cleanroom via an anteroom without **(b)(4)**, exposing the sterile drug product inside the **(b)(4)** to lower than ISO 5 quality air.
3. Your firm engaged in poor aseptic practices during the production of drug products intended to be sterile. Specifically, operators touched a door handle with sterile gloves without disinfecting or changing gloves prior to sterile operations, touched the inner surfaces of the stoppers with a gloved hand while stoppering sterile drug product, and blocked the movement of first air within the ISO 5 hood while working directly over open vials containing sterile drug product.
4. Your firm used non-sterile wipes to clean the ISO 5 areas within the laminar flow hoods and the biosafety cabinet, and disinfectant contact time was inadequate when using a sporicidal agent.

5. Your firm performed surface sampling in the ISO 5 cleanroom after cleaning, rather than before cleaning. Conducting sampling after cleaning may reduce the likelihood of recovering organisms that may have been present during aseptic operations.
6. Your firm failed to perform adequate smoke studies under dynamic conditions to demonstrate unidirectional airflow within the ISO 5 area. Therefore, your products intended to be sterile may be produced in an environment that does not provide adequate protection and poses a significant contamination risk.

Furthermore, the manufacture of the ineligible drug products is subject to FDA's CGMP regulations, Title 21, Code of Federal Regulations (CFR), parts 210 and 211. The FDA investigators observed significant CGMP violations at your facility, causing the ineligible drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations included, for example:

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 cleaning and disinfecting the room and equipment to produce aseptic condition (21 CFR 211.42(c)(10)(v)).
3. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing area (21 CFR 211.42(c)(10)(iv)).
4. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).
5. Your firm failed to ensure that manufacturing personnel wear clothing appropriate to protect drug product from contamination (21 CFR 211.28(a)).

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 and results in the drug being adulterated.

Unapproved New Drug Products

You do not have any FDA-approved applications on file for the ineligible drug products that you compounded.[3] 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. Marketing of these products, or other applicable products, without an approved application violates these provisions of the FDCA.

Misbranded Drug Products

The ineligible drug products you compounded are intended for conditions not amenable to self-diagnosis and treatment by individuals who are not medical practitioners; therefore, adequate directions for use cannot be written 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.[4] Accordingly, these ineligible drug products are misbranded under section 502(f)(1) of the FDCA. The introduction or delivery for introduction into interstate commerce of these products therefore violates section 301(a) of the FDCA. It is also 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 misbranded.

D. Corrective Actions

FDA acknowledges your voluntary recall, initiated on November 17, 2016, of all sterile drug products produced from May 17, 2016, to November 17, 2016, due to lack of sterility assurance. In addition, we acknowledge that your firm ceased sterile drug production on November 22, 2016 and resumed on December 8, 2016. Further, FDA acknowledges the April 17, 2017, Florida Department of Health (FLDOH) order of emergency suspension of your pharmacy permit. Additionally, on May 4, 2017, you voluntarily relinquished your permit pending board action and your firm is no longer operational.

Regarding your response related to the insanitary conditions cited above, the following corrective action appears deficient.

You stated that the transfer of **(b)(4)** with sterile drug product to the **(b)(4)** in another cleanroom was a result of "poor scheduling practices and technician errors" and that your routine practice is using the **(b)(4)** in the same cleanroom. However, it appears that these **(b)(4)** would not be adequately protected when transferred from the laminar flow hoods or biosafety cabinet to the **(b)(4)** in the same cleanroom. You have not conducted smoke studies to demonstrate that the **(b)(4)** remain under the laminar air flow while the vials are being transferred from the ISO 5 areas within the laminar flow hoods or biosafety cabinet into the **(b)(4)**. In addition, your operators wear non-sterile gowning inside this cleanroom. Therefore, these vials are exposed to potential contamination during this transfer, and the sterility assurance is compromised.

For more information on compounding, please see FDA's website, at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm.

Please be aware that section 501(a)(2)(A) of the FDCA concerning insanitary conditions applies regardless of whether drug products you compound meet the conditions of section 503A, including the condition on compounding drug products using a bulk drug substance that complies with an applicable USP or NF monograph, is a component of an FDA-approved human drug, or appears on the 503A bulks list.

As explained above, the compounding of drug products using a bulk drug substance that complies with an applicable USP or NF monograph, is a component of an FDA-approved human drug, or appears on the 503A bulks list is a condition of section 503A, which your firm failed to meet for a portion of the drug products you produced. Should you continue to compound and distribute drug products that do not meet the conditions of section 503A, the compounding and distribution of such drugs would be subject to the new drug approval requirement, the requirement to label drug products with adequate directions for use, and the drug CGMP requirements. Before doing so, you must comply with the requirements of section 505 and 502(f)(1) and fully implement corrections that meet the minimum requirements of the CGMP regulations.[5]

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. 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 produce are neither adulterated nor misbranded. [*See* 21 CFR 210.1(b), 21 CFR 200.10(b)].]

If you resume compounding operations, FDA strongly recommends that your management undertake a comprehensive assessment of operations, including facility design, procedures, personnel, processes, maintenance, materials, and systems. In particular, this review should assess your aseptic processing operations. A third-party consultant with relevant sterile drug manufacturing expertise should assist you in conducting this comprehensive evaluation.

E. 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.

Within fifteen (15) working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct the violations. Please include an explanation of each step being taken to prevent the recurrence of the 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 within fifteen (15) working days, state the reason for the delay and the time within which you will complete the correction.

Electronically mail your written response to John W. Diehl, Director, Compliance Branch, Office of Pharmaceutical Quality Operations, Division 2, at ORAPHARM2_RESPONSES@fda.hhs.gov. Please identify your response with CMS Case # 525312.

If you have questions regarding any issues in this letter, please contact Mr. Diehl at (214) 253-5288.

Sincerely,
/S/
Monica R. Maxwell
Program Division Director
Office of Pharmaceutical Quality Operations,
Division II

[1] We remind you that there are conditions other than those discussed in this letter that must be satisfied to qualify for the exemptions in section 503A of the FDCA.

[2] 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 interim 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 section 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 adequate support 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. GABA, GHRP-2, GHRP-6, and melatonin were nominated for inclusion on the 503A bulks list. They have been identified as substances that were not nominated with adequate support for FDA to evaluate the substance. For additional information, see the guidance at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469120.pdf.

[3] 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.

[4] Your ineligible drug products are not exempted from the requirements of section 502(f)(1) of the FDCA by regulations issued by the FDA (see, e.g., 21 CFR 201.115).

[5] In this letter we do not address whether your proposed corrective actions would resolve the CGMP violations noted above.