Compounded Solutions in Pharmacy 9/18/17

New England District Office
One Montvale Avenue, 4th Floor
Stoneham, MA 02180-3500

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WARNING LETTER
CMS# 532962

September 18, 2017

Michael H. Roberge
Owner and Pharmacist-in-Charge
Compounded Solutions in Pharmacy, LLC
810 Main Street
Monroe, CT 06468-2809

Dear Mr. Roberge:

From February 22, 2017, to March 3, 2017, U.S. Food and Drug Administration (FDA) investigators inspected your facility, Compounded Solutions in Pharmacy, LLC, located at 810 Main Street, Monroe, CT 06468-2809. 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. Additionally, 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 March 3, 2017. Based on this inspection, it appears that you produced drug products that violate the FDCA. FDA acknowledges receipt of your facility's response on March 24, 2017. FDA also acknowledges the statement in your response letter indicating that "as of March 3, 2017, CSP has begun phasing out compounding 'office use only' prescriptions with a completion date of March 25, 2017."

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 practices (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 noted that drug products produced by your firm failed to meet the conditions of section 503A. For example, the investigators collected evidence that indicates:

1. Your firm did not receive valid prescriptions for individually-identified patients for a portion of the drug products you produced.

2. Your firm compounded drug products using rose geranium oil, chloroacetic acid, and m-cresol. Drug products compounded using these bulk drug substances are not eligible for the exemptions provided by section 503A(a), because they 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, the

investigators observed a pharmacist placing their forearms inside the ISO 5 biological safety cabinet while wearing a non-sterile lab coat. In addition, the investigators observed unsealed ceiling tiles in the ISO 7 cleanroom where your ISO 5 biological safety cabinets are located.

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 have ceilings in the aseptic processing areas that are smooth, hard surfaces that are easily cleanable (21 CFR 211.42(c)(10)(i)).

3. Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements (21 CFR 211.67(a)).

4. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

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.

C. Corrective Actions

We have reviewed your firm's responses to the Form FDA 483, dated March 24, 2017. Regarding issues related to the conditions of section 503A of the FDCA, your proposed discontinuation of compounding drugs for office stock appears adequate.

Some of your corrective actions regarding insanitary conditions observed during the inspection appear to be adequate.

We are unable to fully evaluate your corrective action regarding unsealed ceiling tiles in the ISO cleanroom due to a lack of adequate supporting documentation. In response to FDA's observation regarding unsealed ceiling tiles within the ISO 7 cleanroom, you indicated that the tiles were, in fact, sealed with clear sealant. With respect to the chipped and/or peeled caulking observed in the ISO 8 anteroom, you indicated that repairs would be completed by April 10, 2017. However, you have not provided any supporting documentation for us to fully evaluate your corrective actions. Difficult to clean, particle-generating surfaces (such as chipped and/or peeling caulking) in an ISO classified area can increase the risk of product contamination.

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 receipt of a prescription for an identified individual patient prior to compounding and distributing drug products and 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.

Regarding issues related to the conditions of section 503A of the FDCA, your corrective action to discontinue compounding drugs products for office stock appears adequate. FDA acknowledges the statement in your firm's response to the Form FDA 483, indicating that "as of March 3, 2017, CSP has begun phasing out compounding 'office use only' prescriptions with a completion date of March 25, 2017."

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 regulations. 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)].]

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.

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.

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.

Your written notification should refer to the Warning Letter Number above (CMS# 532962). Please address your reply to:

Maya M. Davis, Compliance Officer
U.S. Food and Drug Administration
One Montvale Avenue, 4th floor
Stoneham, MA 02180

If you have questions regarding the contents of this letter, please contact Maya Davis via telephone at 860-240-4289 ex. 25 or via email at Maya.Davis@fda.hhs.gov.

Sincerely,
/S/

Craig W. Swanson
For Diana Amador-Toro
Division Director
Division of Pharmaceutical Quality Operations 1

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[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. M-cresol was nominated for inclusion on the 503A bulks list. It has been identified as a substance that was not nominated with adequate support for FDA to evaluate the substance. Rose geranium oil and chloroacetic acid were not nominated for inclusion on the 503A bulks list. 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.