US Compounding Inc 10/10/17

Office of Pharmaceutical Quality Operations, Division II
4040 N. Central Expressway, Suite 300
Dallas, Texas 75204

October 10, 2017

CMS Case # 510525

WARNING LETTER

VIA UPS EXPRESS

Eddie W. Glover, Pharm.D.
Chief Executive Officer
US Compounding, Inc.
1270 Don's Lane
Conway, Arkansas 72032

Dear Dr. Glover:

You registered with the U.S. Food and Drug Administration (FDA) as an outsourcing facility under section 503B of the Federal Food, Drug, and Cosmetic Act (FDCA) [21 U.S.C. § 353b]**[1]** on December 20, 2013, and again on December 24, 2014, December 31, 2015, and December 15, 2016. From August 10, 2015 to August 21, 2015, and July 6, 2016 to July 15, 2016, FDA investigators inspected your facility, US Compounding, Inc., located at 1270 Don's Lane, Conway, Arkansas 72032. During the July 2016 inspection, 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 facility on August 21, 2015, and on July 15, 2016. FDA acknowledges receipt of your facility's responses, dated October 26, 2015, November 2, 2015, July 28, 2016, and April 19, 2017. FDA also acknowledges your voluntarily recall, initiated on September 21, 2015, of all lots of drug products intended to be sterile that were within expiry due to a lack of sterility assurance.

A. Compounded Drug Products under the FDCA[2]

Under section 503B(b) of the FDCA, a compounder can register as an outsourcing facility with FDA. Drug products compounded by or under the direct supervision of a

licensed pharmacist in an outsourcing facility qualify for exemptions from the drug approval requirements in section 505 of the FDCA [21 U.S.C. § 355(a)], the requirement in section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)] that labeling bear adequate directions for use and the Drug Supply Chain Security Act requirements in section 582 of the FDCA [21 U.S.C. § 360eee-1] if the conditions in section 503B of the FDCA are met.[3]

An outsourcing facility, which is defined in section 503B(d)(4) of the FDCA [21 U.S.C. § 353b(d)(4)], is a facility at one geographic location or address that — (i) is engaged in the compounding of sterile drugs; (ii) has elected to register as an outsourcing facility; and (iii) complies with all of the requirements of this section. Outsourcing facilities must comply with other applicable provisions of the FDCA, including section 501(a)(2)(B) [21 U.S.C. § 351(a)(2)(B)], regarding current good manufacturing practice (CGMP), and section 501(a)(2)(A) [21 U.S.C. § 351(a)(2)(A)], regarding insanitary conditions. Generally, CGMP requirements for the preparation of drug products are established in Title 21 of the Code of Federal Regulations (CFR) parts 210 and 211.

Specific violations are described below.

B. Violations of the FDCA

Adulterated Drug Products

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 [21 U.S.C. § 351(a)(2)(A)]. The investigators observed that your facility was operated in a way that allows the influx of poor quality air into a higher classified area. For example, during both the August 2015 and July 2016 inspections, investigators observed inadequate pressure differentials between rooms of higher quality air and lower quality air. Additionally, during the July 2016 inspection, the investigators observed that your cleanroom was exposed to an unclassified utility area through rough-cut unsealed holes and duct work in the ceiling.

FDA investigators also noted CGMP violations at your facility, that caused your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations include, for example:

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

2. Your firm failed to adequately design the facility with adequate separation or defined areas or such other control systems necessary to prevent contamination or mix-ups (21 CFR 211.42(b)).

3. 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)).

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).

Outsourcing facilities must comply with CGMP requirements under section 501(a)(2)(B) of the FDCA. FDA's regulations regarding CGMP requirements for the preparation of drug products have been established in 21 CFR parts 210 and 211. FDA intends to promulgate more specific CGMP regulations for outsourcing facilities. FDA has issued a draft guidance, *Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act*. This draft guidance, when finalized, will describe FDA's expectations regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 until more specific CGMP regulations for outsourcing facilities are promulgated.

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.

C. Corrective Actions

We have reviewed your facility's responses dated October 26, 2015, November 2, 2015, July 28, 2016, and April 19, 2017, to the Form FDA 483s. We acknowledge your recall of all lots of drug products intended to be sterile that were within expiry due to a lack of sterility assurance on September 11, 2015.

We are unable to fully evaluate the following corrective actions due to lack of adequate supporting documentation:

Your response regarding complaints of abnormal viscosity of your sterile drug products did not include an investigation with a scientifically justified root cause. In addition, your firm changed the **(b)(4)** for these products, but provided no documentation to demonstrate that changes to **(b)(4)** have alleviated viscosity concerns and have no negative impact on product quality.

In your response regarding preservative content testing, you state "USC created a specification that was not based on scientific data to support the specification range." It is not clear whether you have scientific data to support all product specifications.

You did not provide records to support that employee training occurred in response to observed environmental monitoring deficiencies.

We have also received the documentation provided by your firm which describes the completion of construction to your cleanroom areas and installation of an **(b)(4)**. FDA intends to review all supporting documentation and data, as well as the physical changes made to your cleanroom, during a future inspection.

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 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 within 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 Case # 510525**).

Please address your reply to John W. Diehl, Acting Director, Compliance Branch, at the FDA address provided. In addition, please submit a signed copy of your response to john.w.diehl@fda.hhs.gov.

If you have questions regarding the contents of this letter, you may contact Mr. Diehl at (214) 253-5288.

Sincerely,

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

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[1] *See* Pub. L. No. 113-54, § 102(a), 127 Stat. 587, 587-588 (2013).

[2] For information concerning compounded animal drugs, see FDA's Federal Register notice (80 FR 28624, May 19, 2015) announcing the availability of draft guidance for industry (GFI) #230 "Compounding Animal Drugs from Bulk Drug Substances."

[3] We remind you that there are other conditions that must be met to qualify for the exemptions in section 503B of the FDCA. For example, one of the conditions is that bulk drug substances used to compound a human drug product must appear on a list established by the Secretary identifying bulk drug substances for which there is a clinical need ("503B bulks list"), or that appear on the drug shortage list in effect under section 506E of the FDCA at the time of compounding, distribution, and dispensing (section 503B(a)(2)(A)(i) of the FDCA [21 U.S.C. § 353b(a)(2)(A)(i)]). In January 2017, FDA issued a revised final guidance titled, *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act*, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469122.pdf. Under this interim policy, a bulk drug substance that appears in Category 2 or Category 3 (e.g., domperidone) on FDA's website at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467374.pdf cannot be used for compounding consistent with section 503B(a)(2) unless it is used to compound a drug product that appears on FDA's drug shortage list. Additionally, for a compounded drug product to qualify for the exemptions under section 503B, bulk drug substances used to compound it must be manufactured by an establishment that is registered under section 510 (including a foreign establishment that is registered under section 510(i)) (section 503B(a)(2)(A)(i) of the FDCA [21 U.S.C. § 353b(a)(2)(C)]. In addition, for a compounded drug product to qualify for the exemptions under section 503B of the FDCA, it must not appear on the list published by FDA at Title 21 CFR Part 216 of drugs that have been withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective (e.g., drug products containing adenosine phosphate) (section 503B(a)(4) of the FDCA [21 U.S.C. § 353b(a)(4)]).