U.S. FOOD & DRUG ADMINISTRATION
OFFICE OF REGULATORY AFFAIRS
OPQO DIVISION OF PHARMACEUTICAL QUALITY OPS 3

U.S. Food and Drug Administration
Division of Pharmaceutical Quality Operations III
300 River Place, Suite 5900
Detroit, MI 48207
Telephone: (313) 393-8100
Fax: (313) 393-8139
www.fda.gov

Date: July 13, 2018

UPS NEXT DAY
SIGNATURE REQUIRED

CMS Case: 543235

Mr. Gene Kirtser
President and Chief Executive Officer
Resource Optimization & Innovation LLC
645 Maryville Centre Drive, Suite 200
St. Louis, MO 63141-5846

Dear Mr. Kirtser:

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 September 22, 2015, and most recently on December 22, 2016. We acknowledge your de-registration as an outsourcing facility, effective January 3, 2018. From November 7, 2016, to November 29, 2016, an FDA investigator inspected your facility, Resource Optimization & Innovation LLC, located at 2909 North Neergard Avenue, Springfield, MO 65803-6317, prior to your de-registration as an outsourcing facility. Although, as of the date of this letter, your facility is no longer registered as an outsourcing facility, this letter discusses violations identified during the time you were registered as an outsourcing facility.

During the inspection, the investigator noted deficiencies in your practices for producing sterile drug products, which put patients at risk. FDA issued a Form FDA 483 to your facility on November 29, 2016. FDA acknowledges receipt of your facility's responses, dated December 14, 2016, February 1, 2017, and May 31, 2017. Additionally, we acknowledge your correspondence, dated February 19, 2018, informing FDA of your January 3, 2018, de-registration as an outsourcing facility and your business decision to close your 503B sterile compounding division.

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

A. Compounded Drug Products under the FDCA

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. [2]

[1] *See* Pub. L. No. 113-54, § 102(a), 127 Stat. 587, 587-588 (2013).
[2] 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 503B of the FDCA.

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 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

The FDA investigator 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 the aseptic processing area (21 CFR 211.42 (c)(10)(iv)).

2. 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 includes validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

3. Your firm failed to establish a system for cleaning and disinfecting the room and equipment to produce aseptic conditions (21 CFR 211.42(c)(10)(v)).

4. Your firm failed to establish and follow adequate written responsibilities and procedures applicable to the quality control unit (21 CFR 211.22(d)).

5. Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products (21 CFR 211.22(a)).

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

In your responses dated December 14, 2016, February 1, 2017, and May 31, 2017, you described certain corrective actions. After review of your firm's proposed corrective actions and the supporting documentation submitted, it appears you have corrected most of the violations. Additionally, we acknowledge your correspondence, dated February 19, 2018, informing FDA of your January 3, 2018, de-registration as an outsourcing facility and your business decision to close your 503B sterile compounding division. However, we still have concerns with your viable air monitoring procedure.

In response to the inadequate viable air monitoring observation, you indicated that you acquired and validated a volumetric air sampling (SAS) device, and now use it to perform active viable sampling daily, during production. In addition, you indicated that your firm no longer uses settling plates. Moreover, you updated your SOP's to reflect the new procedure. We remain concerned about your firm's ISO 5 action level for viable air monitoring, which, according to SOP 02.ROi.MFr.IVC.030 IVC Environmental Monitoring, is set at (b) (4) . This action level is less stringent than the guidelines stated in the Aseptic Processing Guidance.

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).] These corrective actions are necessary to address the insanitary conditions identified at your facility.

D. Conclusion

The violations cited in this letter are not intended to be an all-inclusive statement of violations identified during the FDA inspection of your facility at the time you were registered as an outsourcing 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.

Within thirty 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 the corrective actions cannot be completed within thirty working days, state the reason for the delay and the time frame within which the corrections will be completed.

Please address your reply via email to: ORAPharm3_Responses@fda.hhs.gov

Eric Mueller, Compliance Officer
U.S. Food and Drug Administration
Division of Pharmaceutical Quality Operations Division III

If you have questions regarding the contents of this letter, please contact Eric Mueller at (402) 331-8536 ext. 101.

Sincerely,

Eric M. Mueller -S

Digitally signed by Eric M Mueller S
DN: c=US o=U S Government ou=HHS ou=FDA ou=People
0 9 2342 19200300 100 1 1=1300161783 cn=Eric M Mueller S
Date: 2018 07 13 09:47:41 05 00'

(Eric Mueller, Acting Director Compliance Branch) for

Nicholas F. Lyons, Director Compliance Branch
U.S. Food and Drug Administration
Division of Pharmaceutical Quality Operations Division III

Cc:

Mr. Tae Sun Kim, Executive Director, Manufacturing and Distribution
Resource Optimization & Innovation LLC
2909 N Neergard Ave
Springfield, MO 65803-6317