FDA U.S. FOOD & DRUG ADMINISTRATION
OFFICE OF REGULATORY AFFAIRS

VIA SIGNATURE CONFIRMED DELIVERY

March 31, 2021

Dr. John D. Musil
Chairman & Founder
Avella of Deer Valley, Inc. Store #38
Currently Registered as Optum Compounding Services, L.L.C.
24416 N 19th Ave., Suite 200
Phoenix, AZ 85085

Dear Dr. Musil:

You registered your facility 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 June 21, 2016, and most recently on October 15, 2020. From April 9, 2018, to April 20, 2018, FDA investigators inspected your facility, Avella of Deer Valley, Inc. #38 (currently registered as Optum Compounding Services, L.L.C.), located at 24416 N 19th Ave., Phoenix, AZ 85085.

During the inspection, the investigators noted that drug products you produced failed to meet the conditions of section 503B of the FDCA necessary for drugs produced by an outsourcing facility to qualify for exemptions from certain provisions of the FDCA. In addition, the investigators 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 April 20, 2018. FDA acknowledges receipt of your facility's responses, dated May 11, 2018, and July 27, 2018. FDA also acknowledges your action on June 15, 2018, to voluntarily recall specific lots of certain compounded intravenous products due to flexible container leaks, and on October 31, 2018, to voluntarily recall one lot of bevacizumab 2.5 mg/0.1 mL prefilled syringe (Lot#138-20182408@58) due to lack of sterility assurance.

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

A. Compounded Drug Products under the FDCA

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

Division of Pharmaceutical Quality Operations IV
19701 Fairchild Road, Irvine, CA 92612-2506
Telephone: 949-608-2900
Fax: 949-608-4417
www.fda.gov

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]

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.

For a compounded drug product to qualify for the exemptions under section 503B, it must be compounded in an outsourcing facility that is in compliance with the registration and reporting requirements in section 503B(b) including the requirement to submit a report to FDA upon initially registering as an outsourcing facility, once in June of each year, and once in December of each year identifying the drug products compounded during the previous 6-month period (section 503B(b)(2) of the FDCA [21 U.S.C. §353b(b)(2)]).

In addition, for a compounded drug product to qualify for the exemptions under section 503B, the labeling of the drug must include certain information (section 503B(a)(10) of the FDCA [21 U.S.C. §353b(a)(10)]).

B. Failure to Meet the Conditions of Section 503B

During the inspection, FDA investigators noted that drug products produced by your facility failed to meet the conditions of section 503B. For example, the investigators noted:

1. Your facility failed to submit a report to FDA upon initial registration as an outsourcing facility in June 2016, identifying the drug products that you compounded during the previous 6-month period.

2. Some of your facility's drug products did not include: the dosage form of the drug on the label, and a list of active and inactive ingredients, identified by established

[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.

name and the quantity or proportion of each ingredient on either the label or the container.

Because your compounded drug products have not met all of the conditions of section 503B, they are not eligible for the exemptions in that section from the FDA approval requirements of section 505, the requirement under section 502(f)(1) that labeling bear adequate directions for use, and the Drug Supply Chain Security Act requirements described in section 582 of the FDCA.

Specific violations are described below.

C. Violations of the FDCA

Adulterated Drug Products

FDA investigators noted CGMP violations at your facility that caused your drug product(s) to be adulterated within the meaning of section 501(a)(2)(B) [21 U.S.C. § 351(a)(2)(B)] of the FDCA. The violations include, for example, that, your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

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 — 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.

Unapproved New Drug Products

You do not have any FDA-approved applications on file for drug products that you compound.[3] Under sections 505(a) and 301(d) of the FDCA [21 U.S.C. §§ 331(d)] a

[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) of the FDCA [21 U.S.C. § 321(p)] because they are not generally recognized as safe and effective for their labeled uses.

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

You compound drug products that 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 causing them to be misbranded under section 502(f)(1) of the FDCA.[4] The introduction or delivery for introduction into interstate commerce of these products therefore violates section 301(a) of the FDCA. Further, 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 and results in the drug being misbranded.

Failure to Report Drugs

As noted above, your facility failed to submit a report to FDA upon initial registration as an outsourcing facility in June 2016, identifying the drug products that you compounded during the previous 6-month period (section 503B(b)(2) of the FDCA). The failure to report drugs by an entity that is registered with FDA in accordance with section 503B(b) is a prohibited act under section 301(ccc)(3) of the FDCA [21 U.S.C. § 331(ccc)(3)].

D. Corrective Actions

We have reviewed your facility's responses to the Form FDA 483 dated May 11, 2018, and July 27, 2018. Although some of your proposed corrective actions appear adequate, we are unable to fully evaluate others due to a lack of adequate supporting documentation. For example, you described the corrective and preventative actions taken to address the incorrect settings on your non-viable particle counter in some ISO 5 hoods and ISO 5 biological safety cabinets, but did not include documentation such as:

- Personnel monitoring results for the excursion period.
- Training records which show that individuals capable of executing changes to alert and action limits to the monitoring system are qualified.

Deficiencies with your investigation into this matter include:

- Your retrospective analysis did not determine a root cause for the non-cleaning related excursions and you relied on environmental monitoring results (viable particulates) to conclude that the implicated lots were not likely to be affected by

[4] Your compounded 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).

the non-viable particle monitoring excursions. Environmental monitoring results are not a direct measure of product sterility or quality.

- Your firm has not indicated if long-term data trend analysis will be conducted moving forward.

Regarding observations related to the conditions of section 503B of the FDCA, your corrective actions appear to be adequate:

> You provided sample drafts of labels that now appear to include all the information in section 503B(a)(10)(A) of the FDCA. Specifically, these labels now include the dosage forms and a list of active and inactive ingredients.[5]

Should you continue to compound and distribute drug products that do not meet the conditions of section 503B, the compounding and distribution of your drugs would be subject to the new drug approval requirement, the requirement to label drug products with adequate directions for use, and the Drug Supply Chain Security Act requirements.

In addition, as explained above, for a compounded drug product to qualify for the exemptions under section 503B, it must be compounded in an outsourcing facility that is in compliance with the registration and reporting requirements in section 503B(b) including the requirement to submit a report to FDA upon initially registering as an outsourcing facility, once in June of each year, and once in December of each year identifying the drug products compounded during the previous 6-month period (section 503B(b)(2) of the FDCA [21 U.S.C. §353b(b)(2)]). Your facility failed to submit a report to FDA in June 2018, identifying the drug products that you compounded during the previous 6-month period.

Further, we note that your firm has been submitting adverse event reports via MedWatch. Adverse event reports must be submitted in an electronic format that FDA can process, review, and archive (21 CFR 310.305(e)(1) (i.e., via the Safety Reporting Portal or Electronic Submissions Gateway). Please refer to the FDA Guidance for Industry, *Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act* for more information.

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

[5] Please note that section 503B(A)(10)(A)(i) of the FDCA specifies that the label of the drug include the statement “This is a compounded drug” or a reasonable comparable alternative statement (as specified by the Secretary) that prominently identifies the drug as a compounded drug. As of the date of this letter, the Secretary has not specified any reasonable comparable alternative statements.

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.

Within thirty (30) 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 thirty (30) working days, state the reason for the delay and the time within which you will complete the correction.

Please send your electronic reply to ORAPHARM4_Responses@FDA.HHS.GOV or mail your reply to:

CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV
U.S. Food & Drug Administration
19701 Fairchild Road
Irvine, California 92612-2506

Please identify your responses with the unique identifier: **CMS 597964**

If you have any questions about the content of this letter, please contact Andrew Haack, Compliance Officer, at 206-340-8212, or to Andrew.Haack@fda.hhs.gov.

Sincerely,

CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV

SP: ah