August 14, 2018

Reference: CMS Case # 552417

UPS OVERNIGHT MAIL
Rebecca M. Shanahan, Chief Executive Officer
Avella Specialty Pharmacy (formerly Advanced Pharma, Inc.)
Corporate Headquarters
24416 North 19th Avenue
Phoenix, Arizona 85085

Ms. Shanahan:

Advanced Pharma, Inc., located at 9265 Kirby Drive, Houston, Texas 77054, 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 January 22, 2014, December 21, 2016, and October 5, 2017. On December 1, 2016, Advanced Pharma was acquired by your firm, Avella Specialty Pharmacy.

From July 11, 2016, to July 22, 2016, an FDA investigator inspected the facility located at 9265 Kirby Drive, Houston, TX 77054-2520, which was owned and operated by Advanced Pharma at the time and is now owned and operated by your firm. During the inspection, the investigator observed that drug products produced by Advanced Pharma failed to meet the conditions under section 503B of the FDCA necessary for drugs produced by an outsourcing facility to qualify for exemptions from certain requirements under the FDCA. In addition, the investigator noted deficiencies in Advanced Pharma's practices for producing sterile drug products, which put patients at risk.

FDA issued a Form FDA 483 to Advanced Pharma on July 22, 2016. FDA acknowledges receipt of Advanced Pharma's response, dated August 8, 2016, and, following its acquisition, your firm's subsequent submission, dated April 21, 2017. Based on this inspection, it appears that drugs that violate the FDCA were produced in this facility.

A. Compounded Drugs under the FDCA

Under section 503B(b), 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

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

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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 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, 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, the FDA investigator noted that drug products produced by your facility failed to meet the conditions of section 503B. For example, the investigator noted that some of your facility's drug products did not include the dosage form of the product on the label. Additionally, for some of the drug products compounded in your facility, a list of active and inactive ingredients, identified by established name and quantity or proportion of each ingredient, did not appear on either the label or the container in accordance with section 503B(b)(10).

Because the drug products compounded in your facility did not meet all of the conditions in section 503B, they are not eligible for the exemptions under section 503B from the FDA approval requirements in 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.

[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. For instance, a drug 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)]).

C. Violations of the FDCA

The FDA investigator noted that drug products compounded in your facility were adulterated due to CGMP violations. See section 501(a)(2)(B) of the FDCA. The violations include, for example:

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

2. Not having, for each batch of drug product purporting to be sterile and/or pyrogen-free, appropriate laboratory testing to determine satisfactory conformance to final specifications for the drug product (21 CFR 211.167(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.

Unapproved New Drug Products

FDA has not approved applications for drug products that were compounded in your facility.[3] Under sections 301(d) and 505(a) of the FDCA [21 U.S.C. §§ 331(d) and 355(a)] a new drug may not be introduced 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.

[3] The specific products made in your facility 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.

Misbranded Drug Products

Drug products that are intended for conditions not amenable to self-diagnosis and treatment by individuals who are not medical practitioners were compounded in your facility. 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 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

We have reviewed your facility's responses, dated August 8, 2016, and April 21, 2017. Most of your corrective actions appear adequate. However, some of your corrective actions appear deficient. Specifically, we remain concerned with your environmental monitoring alert and action limits. In your response dated April 21, 2017, you stated that your rationale for utilizing these alert and action limits is based on the most current standards outlined by the U.S. Pharmacopeia ("USP") Chapter <797>. You indicated that your firm has updated your SOP to reflect the proposed new language to USP Chapter <797> requirements. As an outsourcing facility, you must comply with CGMP requirements under section 501(a)(2)(B) of the FDCA. Samples from ISO5 environments should normally yield no microbiological contaminants. Your firm's current limits do not require action, including assessment of product impact, when any microbial contamination is recovered on the ISO 5 surface or on aseptic operators' gloved fingertips. You should address this concern and perform an impact assessment to evaluate any risk to product intended to be sterile currently on the market.

We are unable to fully evaluate some of your corrective actions due to a lack of adequate supporting documentation. Specifically, in your response dated April 21, 2017, you indicated that you have a trained and qualified microbiologist on staff to conduct validated bacterial endotoxin testing in-house on all epidural finished drug products. However, your response did not include the dosing limits (e.g., maximum recommended bolus dose or, for infusions, the maximum recommended total dose to be administered over a single hour) for all your epidural products. Therefore, we cannot determine if your established endotoxin limits are acceptable.

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

[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).

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).

Regarding observations related to the conditions of section 503B, the following corrective action to your labels appear to be adequate: you state that "Advanced Pharma is in the process of updating its labels to include dosage form of the product and list of active and inactive ingredients, identified by quantity and proportion of each ingredient."

Should you continue to compound and distribute drug products that do not meet the conditions of section 503B of the FDCA, 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.

E. Conclusion

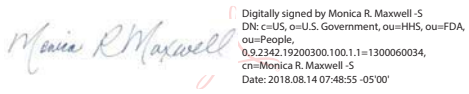
The violations cited in this letter are not intended to be an all-inclusive statement of violations at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to ensure that your firm complies with all requirements of federal law, including FDA regulations.

Within thirty (30) working days of receipt of this letter, you should notify this office in writing of the specific steps 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 (30) working days, state the reason for the delay and the time frame within which the corrections will be completed.

Your written notification should refer to CMS Case 552417. Please submit your reply to John W. Diehl, Director, Compliance Branch, electronically to ORAPHARM2_RESPONSES@fda.hhs.gov. In addition, please submit a signed copy of your response to john.diehl@fda.hhs.gov.

If you have questions regarding the contents of this letter, please contact Mr. Diehl at 214-253-5288, or Mr. Thao X. Ta, Compliance Officer, at 214-253-5217.

Sincerely,



Monica R. Maxwell
Program Division Director
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cc:

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