U.S. FOOD & DRUG ADMINISTRATION
OFFICE OF REGULATORY AFFAIRS
OFFICE OF PHARMACEUTICAL QUALITY OPERATIONS

September 13, 2021

Case #: 608854

VIA Electronic Mail

Kenneth G. Jozefczyk
Director, Centralized Pharmacy Services
BayCare Integrated Service Center, LLC
dba BayCare Central Pharmacy
7802 East Telecom Parkway
Temple Terrace, FL 3637-0928
Kenneth.Jozefczyk@baycare.org

Mr. Jozefczyk:

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 4, 2019, and most recently on December 4, 2020.

From November 18, 2019, to December 10, 2019, an FDA investigator inspected your facility, BayCare Integrated Service Center, LLC dba BayCare Central Pharmacy, located at 7802 East Telecom Parkway, Temple Terrace, FL 33637. During the inspection, the investigator collected evidence indicating 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 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 December 10, 2019. FDA acknowledges receipt of your facility's response dated December 27, 2019 as well as additional correspondence dated April 4, 2020. Based on this inspection, it appears you produced 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

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

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.

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)])].

Further, 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 adverse event reports to FDA "in accordance with the content and format requirements established through guidance or regulation under section 310.305 of title 21, Code of Federal Regulations (or any successor regulations)" (section 503B(a)(1) and (b)(5) of the FDCA [21 U.S.C. §353b(a)(1) and (b)(5)]).

B. Failure to Meet the Conditions of Section 503B

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

1. Some of your facility's drug products did not include the following information on the container: directions for use, including, as appropriate, dosage and administration (see section 503B(a)(10)(B)(iii) of the FDCA). For example, the route of administration is not listed on the container of ephedrine sulfate 25 mg/5 ml.

2. Your facility did not submit adverse event reports to FDA in accordance with the content and format requirements established through guidance or regulation

[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.

under section 310.305 of title 21, Code of Federal Regulations (or any successor regulations)[3]. For example, your documented procedures for reporting adverse events do not describe how you will collect information and investigate adverse events for reporting to FDA and do not outline the adverse event submission process required under 21 CFR 310.305(e).

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

The FDA investigator 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 investigator observed that your firm's facility did not provide a separate, defined, or controlled area for re-packaging of beta lactam and non-beta lactam drug products; and, used a non-dedicated prepacking machine located in an uncontrolled area close to the production area used for compounding of drug products.

The FDA investigator 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 conduct operations related to the manufacture, processing and packing of penicillin in facilities separate from those used for other drug products for human use [21 CFR 211.42 (d)].

2. Your firm failed to establish an adequate system for monitoring environmental conditions in the aseptic processing area [21 CFR 211.42 (c)(10)(iv)].

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

[3] For more information, see, FDA's guidance, "Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act," which can be found at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM434188.pdf.

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 revised 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.

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.

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] 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.

D. Corrective Actions

We have reviewed your facility's response to the Form FDA 483.

Regarding your response related to the insanitary conditions and cGMP observations, we are unable to fully evaluate the adequacy of the following corrective actions due to lack of adequate supporting documentation:

1. You ceased re-packaging of beta-lactam drug products to mitigate the risk associated with potential cross-contamination of other products manufactured and/or repackaged at your firm. However, your response failed to include documentation or supporting information describing how your firm ensured adequate cleaning/decontamination of the non-dedicated re-packaging equipment to remove beta-lactam residues that may potentially result from the repackaging process.

[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).

2. You submitted a validation report assessing the non-viable particle counter equipment performance in relation to the equipment probe orientation (perpendicular to the airflow v (b) (4) or in-line with the laminar air flow). However, you did not include data evidencing challenge of the equipment detection probe using particles having well defined size, refractive index and shape (calibration and verification).

3. You submitted a questionnaire and draft quality agreement for the qualification of your contract test laboratory. However, your response did not address the lack of or include a standardized procedure or policy to select and qualify each of your suppliers.

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).]

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.

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 any violations 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.

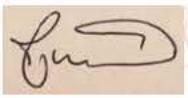
Within thirty (30) working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to address any violations. Please include an explanation of each step being taken to prevent the recurrence of any violations, as well as copies of related documentation. If you believe that your products are not in violation of the FDCA, include your reasoning and any supporting information for our consideration. If you cannot completely address this matter within thirty (30) working days, state the reason for the delay and the time within which you will do so.

Your written notification should refer to case # **608854**.

Please electronically submit your reply, on company letterhead, to Dayna I. Martinez, Compliance Officer, at ORAPHARM2_RESPONSES@fda.hhs.gov. In addition, please submit a signed copy of your response to dayna.martinez@fda.hhs.gov and/or john.diehl@fda.hhs.gov.

If you have questions regarding the contents of this letter, you may contact Dayna I. Martinez via phone at 787-729-8608 or email at dayna.martinez@fda.hhs.gov.

Sincerely,



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