U.S. Food and Drug Administration
Division of Pharmaceutical Quality Operations I
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VIA ELECTRONIC MAIL - READ/DELIVERY RECEIPT

April 27, 2022

Michael Tursi, CEO
Stokes Healthcare, Inc. dba Epicur Pharma
8000 Commerce Parkway, Suite 600
Mt. Laurel, NJ 08054

FEI: 3002815949

Dear Mr. Tursi:

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 January 30, 2018, and most recently on January 20, 2022.

From September 24, 2020, to October 9, 2020, an FDA investigator inspected your facility, Stokes Healthcare, Inc. dba Epicur Pharma, located at 8000 Commerce Parkway, Suite 600, Mt. Laurel, NJ 08054. 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 October 9, 2020. FDA acknowledges receipt of your facility's response dated October 29, 2020, as well as your subsequent communication dated May 5, 2021. 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 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

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

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 on their label the statement "This is a compounded drug." For example, the product labels for Cidofovir Ophthalmic Solution 0.5% and Glycopyrrolate Injectable Solution 0.5 mg/mL did not contain the statement "This is a compounded drug."

2. Your facility did not 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)[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.

[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.
[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.

Specific violations are described below.

C. Violations of the FDCA

Adulterated Drug Products

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

1. Deviations from written production and process control procedures are not justified. [21 CFR 211.100(b)]

2. There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. [21 CFR 211.100(a)]

3. Procedures describing the handling of all written and oral complaints regarding a drug product are not established and followed. [21 CFR 211.198(a)]

4. Time limits are not established when appropriate for the completion of each production phase to assure the quality of the drug product. [21 CFR 211.111]

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.

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.[4] Under sections 505(a) and 301(d) of the FDCA [21 U.S.C. §§ 355(a) and 331(d)] a new drug may not be

[4] 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.

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 use causing them to be misbranded under section 502(f)(1) of the FDCA.[5] 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 firm's response dated October 29, 2020 and subsequent communication dated May 5, 2021. Regarding your response related to time limits for the completion of each production phase, some of your proposed corrective actions appear adequate. However, we cannot fully evaluate the following corrective action described in your response because you did not include sufficient information or supporting documentation:

Your response to the Form FDA 483 states that unlike USP requirements for (b) (4) , cGMP requires data to support processes in sterile manufacturing.

- Your response affirmed that Epicur Pharma's batch processing data do not support a conclusion of a loss of control of your expected processing times and that all processing times are fully documented and reviewed within the batch record as required.
- You also stated that current work practices such as quality review of each step in the process of the batch record and full release testing are part of every product to ensure all parameters are met.
- The investigator noted during the inspection that the executed batch records did not require (b) (4) to document start times for when the material in bulk form was used in compounding, when filling started, and when filling was completed.

It is not clear from your response if you have established a validation plan for bulk holding times. We have not received an updated version for SOP QA-ALL-3007, Master Batch Record, that incorporates parameters for expected processing times as acceptance criteria. It is also unclear if you have established bulk hold times for (b) (4) product (b) (4) of (b) (4) operations.

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

[5] 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).

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).]

In addition, regarding issues related to the conditions of section 503B of the FDCA, some of your corrective actions appear adequate: We have reviewed the revised Standard Operating Procedures (SOPs) you submitted concerning adverse event reporting. These SOPs appear to adequately address how you will collect information and investigate adverse events for reporting to FDA. However, with respect to the adverse event submission process, we note that your SOPs do not establish the submission to FDA of follow-up reports within 15 calendar days of receipt of new information or as requested by FDA [*See* 21 CFR 310.305(c)(2)].

With respect to the 503B drug labeling, FDA expects to evaluate compliance with section 503B(a)(10) upon reviewing copies of any updated labels that you submit in response to this letter.

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.

Lastly, we note that during the inspection, the FDA investigators collected evidence indicating that your firm may be compounding drug products containing cisapride for human use. For a compounded drug product to qualify for the exemptions under section 503B, it must not appear on a 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 ("withdrawn or removed list") (section 503B(a)(4) of the FDCA [21 U.S.C § 353b(a)(4)]).] The withdrawn or removed list at 21 CFR 216.24 lists "all drug products containing cisapride." Thus, if you compound drug products containing cisapride for human use, such drug products would not be eligible for the exemptions provided by section 503B.

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

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 violations, as well as copies of related documentation. This letter notifies you of our concerns and provides you an opportunity to address them. 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.

Please electronically submit your reply, on company letterhead to orapharm1_responses@fda.hhs.gov and Compliance Officer, Juan Jimenez, juan.jimenez@fda.hhs.gov.

Please identify your correspondence with reference number FEI.3002815949.

If you have any questions, contact OPQO Compliance Officer Juan Jimenez at 301-796-1265 or juan.jimenez@fda.hhs.gov.

Sincerely,

Lisa M. Harlan -S Digitally signed by Lisa M. Harlan -S
Date: 2022.04.27 15:51:40 -04'00'

Lisa Harlan
Acting Program Division Director/District Director
U.S. Food and Drug Administration
OPQO Division I / New Jersey District