U.S. FOOD & DRUG ADMINISTRATION

June 17, 2022

Case # 632875

VIA EMAIL
James R. Boswell
President and CEO
LeeSar, Inc.
2727 Winkler Avenue
Fort Myers, FL 33901-9358
(b) (6)

Dear Mr. Boswell:

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 April 30, 2014 and reregistered most recently on December 29, 2021. From October 18, 2021 to October 29, 2021, FDA investigators inspected your facility, LeeSar, Inc., located at 2727 Winkler Avenue, Fort Myers, FL 33901. 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 drug products intended or expected to be sterile, which put patients at risk.

FDA issued a Form FDA 483 to your facility on October 29, 2021. FDA acknowledges receipt of your facility's responses, dated November 17, 2021, January 13, 2022, March 7, 2022 and June 3, 2022. 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

U.S. Food and Drug Administration
Office of Pharmaceutical Quality Operations, Division II
1201 Main Street, Suite 7200
Dallas, Texas 75202
www.fda.gov

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)]).]

Furthermore, 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)]).

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. Some of your facility's drug products, including Azithromycin 500 mg added to Dextrose 5% 250 mL (2 mg/mL), Diltiazem 125 mg added to Dextrose 5% 100 mL (1 mg/mL), Heparin 5,000 units added to NaCl 0.9% 500 mL (10 units/mL), and Vancomycin 1.5 g added to 0.9% NaCl bag 250 mL (6 mg/mL), did not include the following information on the label: the dosage form and a list of active and inactive ingredients, identified by established name and the quantity or proportion of each ingredient (sections 503B(a)(10)(A)(iii)(III) and 503B(a)(10)(A)(iii)(X) of the FDCA).

2. Your facility failed to submit a complete report to FDA in June 2021, identifying all the drug products that you compounded during the previous 6-month period, including Calcium gluconate 1 gm (section 503B(b)(2) of the FDCA [21 U.S.C. §353b(b)(2)]).

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

[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.

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 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 thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed, as required by 21 CFR 211.192. Specifically,

   A. Your firm failed to fully investigate an out of specification (OOS) drug strength test result for Vancomycin 1.5g Lot (b) (4). On 10/26/2020, your contract laboratory reported a result of 89.4%, outside the specifications of (b)(4). You reported this failure as a major deviation in the risk assessment. The quality unit approved this product for release on 10/28/2020 without proper justification to the investigation and there was no additional follow up with any associated batches. This batch was distributed on 10/29/2020 and 10/30/2020.

   B. Your firm failed to identify and investigate an OOS drug strength test result for Vancomycin 1.25g Lot (b) (4) with a result of 89.8% on 09/08/2020 (specification (b)(4)) and the product was approved for release by the quality unit on 09/08/2020 and on 09/18/2020. There was no investigation opened for this OOS result.

   This is a repeat observation. Refer to 2017 FDA 483 Observation 3.

2. Your firm failed to establish adequate control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product, as required by 21 CFR 211.110(a). Specifically, you have not validated the process(es), or equivalent, to demonstrate that the automated system could consistently compound IV bags and syringes within specification for drug strength over multiple lots and days.

3. Your firm failed to include a statement of theoretical yield and yield percentages in the master production and control records, as required by 21 CFR 211.186(b)(7). Specifically,

A. There are no calculations of final batch yield listed in master batch records. An intermediate batch yield is calculated prior to visual inspection. Once product is released or rejected from visual inspection, there are no numbers reported in the batch record to include the final batch quantity and the number of rejected products to establish a final yield of finished products.

B. Calculations used to determine the passing of visual inspection training are not inclusive of the actual number of correctly identified units. Specifically, false positive units are not accounted in current calculation, thus, affecting percent calculations and pass/fail status of training. Recalculation, with the consideration of false positives, revealed that operator (b) (6) does not meet the passing criterion; however, this operator is performing routine visual inspection on current batches of product.

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.[3] 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.

Failure to Report Drugs

As noted above, your facility failed to submit a complete report to FDA in June 2021, 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

[3] 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).

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 evaluated your responses, dated November 17, 2021, January 13, 2022, March 7, 2022, and June 3, 2022.

1. You report that your internal SOP at the time of inspection allowed a (b)(4) , which led to rounding by the Quality Control Unit (QCU) for the two cited incidents in item number 1 above. You state you updated the policy during the inspection, handed it to the FDA investigators as an immediate correction, and the policy has been used from then on. You also report your (b)(4) system provided gravimetric and volumetric accuracy.

   You report that you reviewed OOS procedures and revised the drug strength specification to (b)(4) and (b)(4) and provided a copy of *Process Performance Validation Sterile Operations,* (b)(4) (Attachment 1). You acknowledged the need to expand their QCU and additional training for QCU personnel and you registered for FDA CQCoE trainings on *Investigation and CAPA*, *Environmental Monitoring* and *Regulatory Framework for Human Drug Compounding*. We also note that you committed to conduct comprehensive training, reopen the OOS investigations for root cause analysis by 4/29/2022 and hire additional QCU personnel by 1/31/2022.

   After reviewing your CAPA for item 1 above, you did not address the deficiencies in your OOS investigation and root cause analysis/identification. In addition, you failed to identify the root cause for the significant difference between the (b)(4) machine reported/calculated drug strength (b)(4) and the test result 89.8% reported by (b)(4) Please provide your revised OOS Investigation SOP (policy) or supporting documentation for the (b)(4) systems' validation.

   You failed to address in your responses the safety of (b)(4) lots of Vancomycin 1.5g and 1.25g which have been distributed. Please provide an evaluation of the safety or efficacy of the products distributed.

   You reported in your response that you attributed the OOS relating to drug strength to (b)(4) when the result was received from the contract laboratory. You also reported that you revised your SOP OOS investigations and revised your drug strength specification to (b)(4) . We have reviewed your (b)(4) process validation protocol provided with your response and note that you are still using the " in multiple places, for example, in pages 13 and 17 of 76.

2. In your response to item 2 above, you acknowledged your initial OQ/PQ did not assess (b)(4) for its maximized batch production length. You reported you developed a new process ((b)(4)) protocol with a (b)(4) and

committed to execute the protocol by 6/3/2022. A review of the protocol revealed that it adequately addressed our concern.

We evaluated the data from your process validation of your (b)(4) system provided with your response dated June 3, 2022. We agree with this sampling size; however, you failed to provide the batch records. We note that the (b)(4) evaluated [redacted]; however, you failed to address validating one more lot of each of the products. Although the data you provided shows the automation technology remained in a state of control for (b)(4) lots of each product tested, we do not agree this supports your conclusion that drug strength testing exemption is supported by the (b)(4) until an additional lot of each product is evaluated so that it is statistically meaningful.

3. You explained in your response to item 3 above, that your compounding process master batch record included (b)(4) [redacted]. You admit in your response that these calculations were not readily retrievable. We acknowledge you created a (b) (4) form, and you modified the (b) (4) to include the released quantities. We find you have adequately addressed the deviation in part A of item 3.

   You report that you conducted a review of historical data to establish yield limits for the visual inspection process and revised the (b) (4) SOP in November 2021 as part of the response to the 483 Observations. We evaluated your revised (b) (4) (b) (4) form provided with your response and note that you added a limit of (b)(4) for each of the sample test kits per run as a requirement of the visual inspectors' qualification. Although you begin to address our concerns, we note that you failed to provide the results of your review of historical data to establish yield limits for the visual inspection process. Please provide the justification for the limit changes and your review of the historical data.

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).]

In addition, regarding observations related to the conditions of section 503B of the FDCA, your corrective actions appear adequate:

1. You submitted updated product labels that include the dosage form and a list of active and inactive ingredients, identified by established name and the quantity or proportion of each ingredient.

2. You state that "the June 2021 [product report] submission was updated…with the quantities produced for the missing Calcium Gluconate 1Gm…." You also created a Standard Operating Procedure (SOP) titled, Product Listing and Reporting, to "improve the current recording to be in compliance with the FDA's portal requests."

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 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 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 in which you will do so.

Your written notification should refer to case # 610189. Please electronically submit your reply, on company letterhead, to Mark W. Rivero, Compliance Officer, at ORAPHARM2_RESPONSES@fda.hhs.gov. In addition, please submit a signed copy of your response to mark.rivero@fda.hhs.gov.

If you have questions regarding the contents of this letter, please contact Mr. Rivero at (504) 846-6103.

Sincerely,

Jose R. Lopez Martinez -S Digitally signed by Jose R. Lopez Martinez -S
Date: 2022.06.17 13:07:12 -04'00'

Jose R. Lopez
Acting Director Compliance Branch
Office of Pharmaceutical Quality Operations
Division II