RAM Pharma, Inc 10/27/17

Division of Pharmaceutical
Quality Operations IV
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WARNING LETTER

VIA SIGNATURE CONFIRMED DELIVERY

October 27, 2017

Robert A. Myers
President
RAM Pharma, Inc.
1125 Hollipark Drive
Idaho Falls, ID 83401

Dear Dr. Myers:

You 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 July 21, 2016, and again on December 19, 2016. From February 7, 2017, to March 1, 2017, FDA investigators inspected your facility, RAM Pharma, Inc., located at 1125 Hollipark Drive, Idaho Falls, ID, 83401. 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 serious deficiencies in your practices for producing sterile drug products, which put patients at risk.

FDA issued a Form FDA 483 to your facility on March 1, 2017. FDA acknowledges receipt of your facility's response, dated March 22, 2017. 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 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 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 did not include the statement: "This is a compounded drug" or a statement of quantity or volume on the drug label. In addition, some of your facility's drug products did not include specific information to facilitate adverse event reporting on the container label. Further, some of your facility's drug products did not include a list of active and inactive ingredients on either the drug label or the container label.

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

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 investigators 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 investigators noted that:

1. Your ISO-5 hood is constructed, in part, of unfinished particle board; a particle-generating and difficult to clean material.

2. Your firm produced and released 19 lots of aseptically processed drug products intended to be sterile in an ISO-5 hood that was not tested and certified under dynamic conditions.

3. An employee of your firm was observed operating an industrial service vacuum to clean the floor in the ISO-7 clean room prior to production of sterile compounded drugs.

4. Your firm failed to conduct media fills to simulate aseptic operations.

5. Your firm used non-sterile wipes to clean the inside of the ISO-5 laminar flow hood.

FDA investigators also 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. Your firm failed to ensure a system for maintaining any equipment used to control the aseptic conditions (21 CFR 211.42(c)(10)(vi).

2. Your firm failed to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

3. Your firm failed to ensure a system for cleaning and disinfecting the room and equipment to produce aseptic conditions (21 CFR 211.42(c)(10)(v).

4. Your firm does not have, for each batch of drugs purporting to be sterile and/or pyrogen-free, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product (21 CFR 211.167(a)).

5. Your firm failed to ensure that manufacturing personnel wear clothing appropriate to protect drug product from contamination (21 CFR 211.28(a)).

6. Your firm failed to establish a written testing program designed to assess the stability characteristics of drug products (21 CFR 211.166(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 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 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 an initial report upon registration as an outsourcing facility in July, 2016, and a complete report to FDA in December 2016, identifying the drug products that you compounded during the previous 6-month period (section 503B(b)(2) of the FDCA). The report that your facility submitted in December 2016 was incomplete because it underreported the units of certain products produced (e.g., vancomycin 1000 mcg / 0.1 mg and ceftazidimide 2250 mcg / 0.1 mL). 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 firm's March 22, 2017, response to the Form FDA-483.

Regarding the insanitary conditions and CGMP observations observed during this inspection, some of your corrective actions appear inadequate.

1. Your response states the particle board affixed to your ISO-5 hood is part of the “inner workings” of the hood and not part of an exposed surface. However, the material presents a contamination risk as it is not easily cleanable and can shed particles. It is not suitable within an ISO-7 clean room, and in such close proximity to the critical ISO-5 work surface.

2. Your response states that you have discontinued the use of the vacuum for cleaning the ISO-7 clean room. However, it does not address the operator’s failure to change their gloves or sanitize their gloved hands.

We are unable to fully evaluate the following corrective actions due to a lack of adequate supporting documentation:

1. Your response indicated you will certify the ISO-5 hood at least every six months, and prior to the certification expiration date. However, your existing procedures already require certification “at least every six months.” Your response does not describe, specifically, how you will ensure the hood remains certified. Additionally, your response fails to indicate whether a product impact assessment will be performed for sterile products released during the period that the hood was not certified.

2. Your response indicates you will follow existing procedures requiring personnel to complete media fills for “low,” “medium,” and “high” risk processes, and that the first such media fill will be done May 01, 2017. However, your response does not address whether sterile drug production was permitted prior to May 01, 2017, or whether personnel are prohibited from sterile drug production activities until the successful completion of media fills.

3. Your response stated that you have revised your procedures to require the use of sterile wipes for cleaning the ISO-5 hood. However, review of SOP # 05-001 “Clean Suite Cleaning and Sanitizing Operations” indicates that it does not explicitly describe your cleaning agents’ attributes (i.e. whether they are sterile and/or sporicidal); and does not specify which cleaning agents are to be used on the various surfaces within your classified areas, or at what frequency. Additionally, your response notes the addition of a sporicidal agent to the cleaning regimen, but does not specify its name or directions for use (e.g. contact time).

4. Your response indicates all sterile drug products will be tested for sterility and bacterial endotoxins, and that products cannot be released until the successful completion of a 14-day sterility test. However, SOP # 10-006 “Finished Product Endotoxin Testing” is inadequate as it does not explicitly require all batches of drug product purporting to be pyrogen-free to be tested for bacterial endotoxins. Additionally, you did not include an updated copy of your sterility testing procedure (SOP # 10-005). Consequently, its adequacy cannot be evaluated.

5. Your response indicates that gowning procedures have been updated to require “sterile gowning materials.” However, SOP # 09-003 “Cleanroom Gowning” does not require the use of sterile shoe covers; sterile face mask/beard covers.

6. Your response states that you have developed technical protocols to study the sterility of lidocaine 1%/phenylephrine 1.5% injection, and; oxytocin 30U/500ml normal saline. However, you failed to provide any data to support your contention that these products retain their labeled potency, and remain sterile and pyrogen-free over their current beyond-use-dating period (BUD). Furthermore, you did not commit to conducting stability studies for all sterile drugs you produce.

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).]

Regarding the observations related to the conditions of section 503B of the FDCA, some of your corrective actions appear adequate. You state that you have updated your labels to include all of the required information, and provided samples. However, the sample container label does not include directions for use. In addition, you have implemented and provided a copy of your SOP 12-002. The SOP does not include all of the labeling information required by section 503B(a)(10) of the FDCA, such as the name, address, and phone number of your outsourcing facility, and the date the drug was compounded, among others. You should address these concerns, and revise your SOP accordingly.

Further, to address the underreporting and recording of all units produced, you implemented and provided a copy of SOP 14-001. This appears adequate.

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.

FDA strongly recommends that your management first 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 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.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure and injunction.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Please include an explanation of each step being taken to prevent the recurrence of 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 15 working days, state the reason for the delay and the time within which you will complete the correction.

Your written notification should refer to the Warning Letter Number above (**526405**). Please address your reply to:

CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV
United States Food and Drug Administration
19701 Fairchild
Irvine, California 92612-2506

If you have questions regarding the contents of this letter, please contact Maria P. Kelly-Doggett, Compliance Officer, via email to maria.kelly-doggett@fda.hhs.gov or by phone at (425) 302-0427 and reference unique identifier **526405.**

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

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[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.

[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).