Apollo Care 3/20/19

U.S. FOOD & DRUG ADMINISTRATION

Division of Pharmaceutical
Quality Operations III
300 River Place, Suite 5900
Detroit, MI 48207
Telephone: (313) 393-8100
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March 20, 2019

WARNING LETTER

Case# 574756

UPS NEXT DAY
SIGNATURE REQUIRED

James M. Krogman, President and Co-Owner
Apollo Care, LLC
3801 Mojave Court, Suite 101
Columbia, MO 65202

James Harasha, Co-Owner Apollo Care LLC
1200 N. Mayfair Rd., Suite 260,
Wauwatosa, Wisconsin, 53226

Dear Mr. Krogman and Mr. Harasha:

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 September 14, 2017 and re-registered on November 21, 2018. From February 12, 2018, to March 13, 2018, an FDA investigator inspected your facility, Apollo Care LLC, located at 3801 Mojave Court, Suite 101, Columbia, MO 65202. During the inspection, the investigator 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 investigator 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 13, 2018. FDA acknowledges receipt of your facility's response, dated March 27, 2018. FDA also acknowledges your action on February 15, 2018, to voluntarily recall two lots of Vancomycin HCl IV injectable product and your action on March 7, 2018, to voluntarily recall two additional lots of Vancomycin HCl IV injectable product. 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 investigator noted that drug products produced by your facility failed to meet the conditions of section 503B. For example, the investigator noted:

1. Some of your facility's drug products did not include the following statements on the label: the dosage form of the drug; the date that the drug was compounded; and storage and handling instructions.

2. Your facility failed to submit a report to FDA upon initial registration, identifying the drug products that you compounded during the previous six-month period.

3. Your facility failed to submit complete reports in December 2017 and in June 2018, identifying all of the drug products that you compounded during the previous six-month period. For example, the reports failed to include 8.4% sodium bicarbonate (1 mEq/mL) 50 mL syringe.

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:

1. Your firm continued aseptic production within ISO 5 laminar air flow (LAF) hoods despite identifying multiple HEPA filter leaks within the surrounding ISO 7 cleanroom during certifications.

2. Dirt/debris was observed on the top of **(b)(4)** ISO 5 LAF hoods.

3. Your firm performed aseptic production within multiple ISO 5 LAF hoods with laminate work surfaces. Moreover, cracks and chips were observed at the edges of the laminate surfaces. Laminate material is difficult to clean and may harbor microbial contamination.

4. Your firm failed to perform adequate smoke studies under dynamic conditions to demonstrate unidirectional airflow within the ISO 5 area. Therefore, your products intended to be sterile are produced in an environment that may not provide adequate protection against the risk of contamination.

5. Your firm's aseptic operators had not completed any successful media fills before initiating aseptic production. In addition, your firm's media fills were not performed under the most challenging or stressful conditions. Therefore, there is a lack of assurance that your firm can aseptically produce drug products within your facility.

The FDA investigator 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 establish adequate written responsibilities and procedures applicable to the quality control unit and to follow such written procedures (21 CFR 211.22(d)).

2. Your firm failed to establish and follow appropriate written procedures that are 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 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 (21 CFR 211.192).

4. Your firm failed to maintain the buildings used in the manufacture, processing, packing, or holding of a drug product in a clean and sanitary condition (21 CFR 211.56(a)).

5. Your firm failed to prepare batch production and control records with complete information relating to the production and control of each batch of drug product produced (21 CFR 211.188).

6. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

7. Your firm failed to ensure that each person engaged in the manufacture, processing, packing, or holding of a drug product has the education, training, and experience, or any combination thereof, to enable that person to perform his or her assigned functions (21 CFR 211.25(a)).

8. Your firm failed to routinely calibrate, inspect, or check according to a written program designed to assure proper performance and to maintain written records of calibration checks and inspections of automatic, mechanical, or electronic equipment, including computers, used in the manufacture, processing, packing, and holding of a drug product (21 CFR 211.68(a)).

9. Your firm failed to establish and follow written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures (21 CFR 211.80(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 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] 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.

Failure to Report Drugs

As noted above, your facility failed to submit a report to FDA upon initial registration as an outsourcing facility in September 2017, and in December 2017 and June 2018, your facility failed to submit a report identifying all 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 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 facility's response to the Form FDA 483. We acknowledge your recall of Vancomycin HCl IV injectable, Lots AC-015558 and AC-015560 on February 15, 2018, and Lots AC-015569 and AC-015565 on March 7, 2018 due to stability concerns.

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

1. In regard to your procedures applicable to your quality unit, you committed to hiring an "employee that has expertise in quality control and more importantly cGMP." In the interim, you planned to utilize "outsource consultants with the authority to approve or reject all procedures and/or specifications impacting the identity, strength, quality, and purity of the drug product." However, you did not provide the time frame for the hiring. In addition, you did not provide supporting documentation such as:

a. Detailed information or SOP on the responsibility of these consultants and/or Apollo Care's "Managing Member."
b. The updated SOPs to "reflect the correct SOP or operating form."
c. The training records for all revised SOPs.
d. The SOP for complaint review, documentation, investigations, corrective and preventative actions.
e. The SOP INST002.1 for Labeling requirements or the master file for labels.
f. Invoice of the "appropriate Visual Inspection equipment" and information to demonstrate its meets the intended purpose and any training documents for this new equipment.

2. In regard to the establishing and following appropriate written procedures that are designed to prevent microbiological contamination, you committed to conducting a media fill and smoke study, mixing and weighing in the ISO 8 classified area, developing SOP to document HEPA filter leaks, and SOP pertaining to the depyrogenation cycle. However, you did not provide supporting documentation such as:

a. The Media fill protocol or most recent media fill report.
b. Detailed smoke study report or video, if taken.
c. Revised SOP requiring weighing and mixing be performed in an ISO 8 classified area.
d. Deviation SOP regarding HEPA filter leaks.
e. The validation report showing the effectiveness of your depyrogenation cycle.

3. In regard to unexplained discrepancy or failure of a batch, you "agreed to a service level agreement" with the third-party laboratory that any out of specification (OOS) results are reported "in accordance with the FDA Guidance." You also committed to developing SOPs pertaining to the "OOS process" and deviations. However, you did not provide the service agreement with the contractor lab or the SOPs. In addition, you did not provide the investigation report for the failed stability test for the Vancomycin HCl, or if beyond use date for this product has been modified due to the stability results.

4. In regard to the maintenance of the hoods and buildings used for production, your firm committed to **(b)(4)** cleaning of the exterior of the ISO 5 hoods, addressing the cracks on the hoods, and to regularly checking for "scratches, paint chips and rust" in production areas. However, you did not provide supporting documentation such as:

a. Your revised cleaning SOP, logs, and training records.
b. Pictures or invoices demonstrating the scratches, chips, rust, and unsealed power poles have been repaired.
c. Description and schedule on how "all caulking and sealing will be regularly checked for compliance."

5. In regard to the batch production and control records, your firm committed to reviewing "all batch and production records" prior to distribution and implementing a label review log as part of SOP Labeling requirement. However, you did not provide supporting documentation such as:

a. Staff training records on the completeness and correctness of batch records.
b. Details of "correct applicable information" that will be recorded on the batch and production records including any revised master batch records to document the

additional information being reviewed.

6. In regard to the monitoring of environmental conditions, you committed to include “all carts and shelves” as “part of the regular rotation of monitoring that occurs during production.” In addition, you will be using a “deviation SOP” for documenting and investigating “environmental monitoring excursions.” However, you did not provide supporting documentation such as revised environmental monitoring SOP, Deviation SOP, and training records for these SOPs.

7. In regard to the education and training, you committed to documenting staff competency. However, you did not provide supporting documentation such as completed staff competencies and training plan for competencies.

8. In regard to the calibration and maintenance, you committed to developing “a calibration and maintenance SOP.” However, you did not provide supporting documentation such as recent calibration records, and SOP’s for equipment calibration including the schedule for calibration for the equipment at the firm.

9. In regard to components and drug product containers and closures, you committed to identifying an “area for quarantined product” with the intention “to quarantine all products upon receipt until the appropriate certificate analysis is obtained.” In addition, you stated that “appropriate measures have been taken to ensure that all received product are stored off the floor and suitably spaced.” However, you did not provide supporting documentation such as an SOP detailing this policy or the “appropriate measures” that have been taken to ensure all materials received are stored off the floor. Furthermore, you did not address the temperature monitoring in the warehouse and the storage requirements for materials being received and stored within the warehouse area.

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, we are unable to fully evaluate corrective actions regarding product label issues due to lack of adequate supporting documentation. Specifically, you stated that all required information on your labels are now included, “Apollo Care provided to [the investigator] at her request…with the corrections made,” and that “the newly drafted

Labeling Requirements SOP outlines all required information and the Label Review Log documents successful application of said labels." To date, we have only received your updated product label for vancomycin 1.25 g added to 250 mL of 0.9% sodium chloride. We have not yet received your other corrected labels or your Labeling Requirements SOP.

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 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 (15) 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.

Please send your electronic reply to: ORAPHARM3_RESPONSES@fda.hhs.gov.

Attn: Eric Mueller
Compliance Officer

U. S. Food and Drug Administration
Division of Pharmaceutical Quality Operations III

Refer to the Unique Identification Number (Case# 574756) when replying. If you have questions regarding the contents of this letter, please contact Eric Mueller, Compliance Officer, at (402) 331-8536 ext. 101.

Sincerely,
/S/
Art O. Czabaniuk
Program Division Director
Division of Pharmaceutical Quality Operations III

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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).

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