Pharmacy Resources Incorporated 3/1/18

Division of Pharmaceutical
Quality Operations IV
19701 Fairchild Road, Los
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WARNING LETTER

VIA SIGNATURE CONFIRMED DELIVERY

March 1, 2018

Gregg N. Pederson, President
Pharmacy Resources, Inc.
5290 E. Yale Circle, Suite 101
Denver, CO 80222

Dear Mr. Pederson:

From May 8, 2017, to May 23, 2017, a U.S. Food and Drug Administration (FDA) investigator inspected your facility, Pharmacy Resources Inc., located at 5290 E. Yale Circle, Suite 101, Denver, CO 80222. During the inspection, the investigator noted that drug products you produced failed to meet the conditions of section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA) [21 U.S.C. § 353a] for exemption 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.

A Form FDA 483 was issued to your firm on May 23, 2017. We acknowledge receipt of your written response, dated June 8, 2017. Based on this inspection and a review of your response, it appears that you produced drug products that violate the FDCA.

A. Compounded Drug Products Under the FDCA

Section 503A of the FDCA describes the conditions under which human drug products compounded by a licensed pharmacist in a State licensed pharmacy or a Federal facility, or a licensed physician, qualify for exemptions from three sections of the FDCA: compliance with current good manufacturing practices (CGMP) (section 501(a)(2)(B)); labeling with adequate directions for use (section 502(f)(1)); and FDA approval prior to marketing (section 505) [21 U.S.C. §§ 351(a)(2)(B), 352(f)(1) and 355].[1] Receipt of valid prescriptions for individually-identified patients is one of the conditions for the exemptions under section 503A.

B. Failure to Meet the Conditions of Section 503A

During the inspection, the FDA investigator noted that drug products produced by your firm failed to meet the conditions of section 503A. For example, the investigator noted your firm did not receive valid prescriptions for individually-identified patients for a portion of the drug products you produced.

Therefore, you compounded drug products that do not meet the conditions of section 503A and are not eligible for the exemptions in that section from the FDA approval requirement of section 505 of the FDCA, the requirement under section 502(f)(1) of the FDCA that labeling bear adequate directions for use, and the requirement of compliance with CGMP under section 501(a)(2)(B) of the FDCA. In the remainder of this letter, we refer to your drug products that do not qualify for exemptions under section 503A as the "ineligible drug products."

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 failed to use adequate contact times for sporicidal agents used as part of your disinfection program for the aseptic processing area.

2. 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 may be produced in an environment that does not provide adequate protection and poses a significant contamination risk.

Furthermore, the manufacture of the ineligible drug products is subject to FDA's CGMP regulations, Title 21, Code of Federal Regulations (CFR), parts 210 and 211. The FDA investigator observed significant CGMP violations at your facility, causing the ineligible drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations included, for example:

1. Your firm failed to establish an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions. 21 CFR 211.42(c)(10)(v)

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

3. 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)

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

5. Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. 21 CFR 211.160(b)

6. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of such stability testing to determine appropriate storage conditions and expiration dates. 21 CFR 211.166(a)

7. Your firm failed to ensure that routine calibration of equipment is performed according to a written program designed to assure proper performance. 21 CFR 211.68(a)

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

The ineligible drug products you compounded 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.[2] Accordingly, these ineligible drug products are misbranded under section 502(f)(1) of the FDCA. 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 firm's response to the Form FDA 483. Regarding the insanitary condition observations in the Form FDA 483, some of your corrective actions appear to be adequate. However, we cannot fully evaluate the adequacy of

the following corrective actions described in your response because you did not include sufficient information or supporting documentation:

1. Your response did not include any supporting documentation related to the review and revision of your cleaning procedure to address the inadequate contact time you use for sporicidal agents.

2. Your response did not include a copy of the video or a detailed report describing the conditions of the smoke studies for our review. No details were provided with the response as to the nature of the activities to be conducted to simulate dynamic conditions. Therefore, you have not demonstrated that unidirectional airflow is maintained while personnel are working in the ISO 5 areas.

Regarding the observation related to personnel gowning, we remain concerned that the reuse of the **(b)(4)** suit poses a direct contamination risk to the ISO 5 aseptic processing area as the sleeves of the suit would cross into the ISO 5 area during aseptic processing. Your response does not include any actions to mitigate this potential contamination risk. In addition, your response received does not address the issues regarding the adequacy of your in-house sterility testing method.

Please be aware that section 501(a)(2)(A) of the FDCA concerning insanitary conditions applies regardless of whether drug products you compound meet the conditions of section 503A, including the condition on receipt of a prescription for an identified individual patient prior to compounding and distributing drug products.

Should you continue to compound and distribute drug products that do not meet the conditions of section 503A, the compounding and distribution of such drugs would be subject to the new drug approval requirement, the requirement to label drug products with adequate directions for use, and the drug CGMP regulations. Before doing so, you must comply with the requirements of section 505 and 502(f)(1) and fully implement corrections that meet the minimum requirements of the CGMP regulations.[3]

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)].

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.

Your written notification should refer to the Warning Letter Number above (**547385**). Please address your reply to:

CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV
U.S. Food & Drug Administration
19701 Fairchild
Irvine, California 92612

If you have questions regarding any issues in this letter, please contact Matthew R. Dionne, Compliance Officer, via email at Matthew.Dionne@fda.hhs.gov or by phone at (303) 236-3064 and reference unique identifier **547385**.

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

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[1] 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 503A of the FDCA.

[2] Your ineligible 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).

[3] In this letter we do not address whether your proposed corrective actions would resolve the CGMP violations noted above.