Snyder Mark Drugs Roselle, Inc. d.b.a. Mark Drugs Pharmacy 2/27/18

Division of Pharmaceutical
Quality Operations III
300 River Place. Suite 5900
Detroit, Ml 48207
Telephone: (313) 393-8100
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February 27, 2018

WARNING LETTER

Case# 547409

UPS NEXT DAY
SIGNATURE REQUIRED

Mark H. Mandel
Owner and Pharmacist-in-Charge
Snyder Mark Drugs Roselle, Inc.
dba Mark Drugs Pharmacy
384 E. Irving Park Road
Roselle, IL 60172-2007

Dear Dr. Mandel:

From April 26, 2017, to May 22, 2017, U.S. Food and Drug Administration (FDA) investigators inspected your facility, Snyder Mark Drugs Roselle, Inc., dba Mark Drugs Pharmacy, located at 384 E. Irving Park Road, Roselle, IL 60172-2007. During the inspection, the investigators 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 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 firm on May 22, 2017. FDA acknowledges receipt of your facility's response, dated June 13, 2017. Based on this inspection, 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 practice (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(a)].[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 investigators noted that drug products produced by your firm failed to meet the conditions of section 503A. Specifically, the investigators noted your firm did not receive valid prescriptions for individually-identified patients for a portion of the drug products you produced.

Therefore, your compounded drug products that do not meet the conditions of section 503A and are not eligible for the exemptions 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 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 observed that:

1. An operator blocked unidirectional airflow to sterile syringe tips and uncapped final product containers during aseptic production in the ISO 5 **(b)(4)**.

2. An operator failed to sanitize gloves after handling non-sterile active pharmaceutical ingredients (API) before handling sterile materials during aseptic production.

3. Operators wore non-sterile gloves while **(b)(4)** loading **(b)(4)** vials containing sterile product into a lyophilizer and loading materials into the ISO 5 **(b)(4)**.

4. Operators transferred **(b)(4)** vials from an ISO 5 **(b)(4)** to a lyophilizer located in the **(b)(4)**, exposing the sterile drug product within the vials to worse than ISO 5 classified air.

5. Your firm failed to adequately monitor pressure differentials between classified and unclassified areas to ensure proper airflow.

6. Your firm failed to demonstrate through appropriate studies that your **(b)(4)** is able to provide adequate protection of the ISO 5 area in which sterile products are processed. Therefore, your products may be produced in an environment that 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 investigators 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 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)).

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

3. Your firm failed to establish an adequate system for maintaining equipment used to control the aseptic conditions (21 CFR 211.42(c)(10)(vi)).

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

5. Your firm does not have, for each batch of drug product 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)).

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)).

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 the ineligible drug products that you compounded.[2] Under sections 505(a) and 301(d) of the FDCA [21 U.S.C. § 331(d)], a new drug may not be 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

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.[3] Accordingly, these ineligible drug products are misbranded under section 502(f)(1) of the FDCA. The introduction or delivery for introduction into interstate commerce of these products therefore violates section 301(a) of the FDCA. 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 to the Form FDA 483. Regarding your response related to the insanitary conditions cited above, some of your corrective actions appear to be adequate. However, the following corrective actions appear to be deficient:

1. Your response states that a **(b)(4)** will be purchased and installed. However, your response does not indicate a timeframe for implementation or any appropriate interim actions. We remain concerned that **(b)(4)** drug products intended to be sterile will continue to be handled in your laminar airflow workbench, which houses your lyophilizer, that has not been demonstrated to meet ISO 5 classification. In addition, your response fails to address the exposure of the **(b)(4)** vials to worse than ISO 5 quality air during the transfer from the **(b)(4)** to the lyophilizer in the laminar airflow workbench.

2. Your response does not commit to routine monitoring of the pressure differentials between the **(b)(4)** and **(b)(4)** where **(b)(4)** doorways were observed by investigators to separate these areas. Measuring of pressure differentials is critical to ensure proper airflow from areas of higher quality air to adjacent areas with lower quality air.

3. Although your response states that no corrective actions are warranted related to the smoke pattern testing of the ISO 5 **(b)(4)**, the conditions under which a smoke pattern test was conducted for your **(b)(4)** were not specified in the certification report. Therefore, you have not demonstrated that unidirectional airflow is maintained while personnel are working in the ISO 5 area.

We are unable to fully evaluate the adequacy of the following corrective actions described in your response due to a lack of adequate supporting documentation:

1. Your response states that your operators will be retrained on proper aseptic technique, but no supporting documentation was provided for our review.

2. Regarding the Form FDA 483 observation about the handling of non-sterile API, your response failed to include sufficient detail about the proposed changes related to the **(b)(4)** or **(b)(4)** of API. In addition, the revised policy and procedure referenced in your response was not submitted for our review.

3. Your response states that you will purchase sterile powder-free **(b)(4)** gloves in individual packages and, you retrained staff to don these sterile gloves at all times when working in the **(b)(4)** as well as when handling materials in the ISO 5 classified **(b)(4)**. However, supporting documentation related to staff retraining and revised policies related to sterile gloves, including cleaning of the **(b)(4)**, was not submitted for our review. In addition, your response includes a proposed corrective action related to the changing of sterile gloves on the ISO 5 **(b)(4)** at least every **(b)(4)** during continuous processes. However, we are concerned with this practice occurring during continuous processing as it may increase the risk of contaminating exposed product within the **(b)(4)**.

4. Regarding the Form FDA 483 observation about the inadequate sterility and pyrogen testing, your response states that additional testing would be periodically conducted on intrathecal drug products. However, no additional details (i.e., type of testing and frequency) or supporting documentation related to this commitment was provided for our review.

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.

As explained above, receipt of valid prescriptions for individually-identified patients is a condition of section 503A, which your firm failed to meet for a portion of the drug products you produced. 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 requirements. 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.[4]

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 the violations. Please include an explanation of each step being taken to prevent the recurrence of the 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 fifteen (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: Russell K. Riley
Compliance Officer
U. S. Food and Drug Administration
Division of Pharmaceutical Quality Operations III

Refer to the Unique Identification Number (Case# 547409) when replying. If you have questions regarding the contents of this letter, please contact Mr. Riley by phone at (312) 596-4219.

Sincerely,
/S/
Nicholas F. Lyons
Compliance Director
Division of Pharmaceutical Quality Operations III

for
Art O. Czabaniuk
Program Division Director
Division of Pharmaceutical Quality Operations III

[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] 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) [21 U.S.C. 321(p)] of the FDCA because they are not generally recognized as safe and effective for their labeled uses.

[3] 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).

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