Boothwyn Pharmacy LLC 7/25/18

Division of Pharmaceutical Quality
Operations I
10 Waterview Blvd, 3rd FL
Parsippany, NJ 07054
Telephone: (973) 331-4900
FAX: (973) 331-4969

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER
CMS# 560524

July 25, 2018

Mr. Louis M. Micolucci, President/CEO
Boothwyn Pharmacy, LLC
221 Gale Lane
Kennett Square, PA 19348

Dear Mr. Micolucci:

From June 5, 2017, to June 16, 2017, a U.S. Food and Drug Administration (FDA) investigator inspected your facility, Boothwyn Pharmacy, LLC, 221 Gale Lane, Kennett Square, PA 19348. 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.

FDA issued a Form FDA 483 to your firm on June 16, 2017. FDA acknowledges receipt of your facility's response, dated July 7, 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 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(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 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.

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, the investigator observed:

1. The pharmacist reached over open vials obstructing airflow in the ISO 5 biological safety cabinet (BSC) on multiple occasions during aseptic processing.

2. The pharmacist exposed depyrogenated vials, sterilized rubber stoppers, and syringes to lower than ISO 5 quality air prior to transferring into the ISO 5 area within the BSC during aseptic processing.

3. Your firm used cleaning pads or wipes in the ISO 5 aseptic processing areas that are not sterile.

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 an environment that may not provide adequate protection against the risk of contamination.

5. Your media fills were not performed under the most challenging or stressful processing conditions. Therefore, there is a lack of assurance that your firm can aseptically produce drug products within your facility.

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

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

4. 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)).

5. Your firm failed to follow a 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)).

6. Your firm failed to routinely calibrate, inspect, or check according to a written program designed to assure proper performance 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)).

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 responses to the Form FDA 483.

Regarding some of the insanitary condition observations in the Form FDA 483, 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. In your response, you indicated that you will be "retraining personnel in the proper technique to avoid obstructing air flow" within the ISO 5 hood during aseptic processing. However, you did not provide any documentation to support this corrective action.

2. In your response, you indicated that you have revised your SOPs "to state that the technician or pharmacist will open foil coverings in the ISO class 5 area and to ensure depyrogenated glass vial containers are wiped with a sterile IPA 70% wipe prior to entry into an ISO class 5 area" and that personnel will be retrained in these techniques. However, you did not provide any documentation to support this corrective action.

3. In your response, you indicated that you have "replaced all non-sterile wipes and mini mop covers with sterile wipes and sterile cleaning pads (including but not limited to mop heads)." Your firm provided a copy of the packaging for the sterile wipes purchased; however, you did not provide any documentation regarding mop covers to support this corrective action.

Regarding other observations related to insanitary conditions, the following corrective actions appear deficient:

1. Your firm did not perform or commit to performing a new smoke study that would include all areas within the ISO 5 biological safety cabinet.

2. Your firm indicated that you would use the "largest" batch size to simulate the media fill. However, the media fill documents indicated that you will be challenging your process using only 6 vials and the simulation does not reflect your actual process.

In addition, our review of the documents collected during the inspection revealed that for your product Myers Cocktail Injection, the COA for the ingredient Calcium Gluconate, USP (Anhydrous, batch/lot number 128749) states "Not for injectable use." Using an ingredient that is not suitable for its intended use could impact the quality and safety of the finished product.

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.

Also, 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 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.[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 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 (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 fifteen (15) working days, state the reason for the delay and the time within which you will complete the correction.

Your e-mailed or written notification should refer to the Warning Letter Number above (CMS# 560524) Please address your reply to:

Yvette Johnson
Compliance Officer
Food and Drug Administration
U.S. Customhouse
2nd and Chestnut Sts.
Philadelphia, PA 19106

If you have questions regarding the contents of this letter, please contact Yvette Johnson at 215-717-3077, or by e-mail at Yvette.Johnson@fda.hhs.gov.

Sincerely,
/S/
For: Diana Amador Toro
Division Director/OPQ Division1
New Jersey District Office

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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] 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.