Crosbys Drugs Inc 11/30/17

Division of Pharmaceutical
Quality Operations III
300 River Place, Suite 5900
Detroit, MI 48207
Telephone: (313) 393-8100
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November 30, 2017

WARNING LETTER

Case # 536189

UPS NEXT DAY
SIGNATURE REQUIRED

Sherrie L. Cohen-Merchant, Owner
Crosby's Drugs Inc.
2609 North High Street
Columbus, OH 43202-2555

Dear Ms. Cohen-Merchant:

From September 12, 2016, to September 16, 2016, a U.S. Food and Drug Administration (FDA) investigator inspected your facility, Crosby's Drugs Inc., located at 2609 North High Street, Columbus, OH 43202-2555. 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 September 16, 2016. FDA acknowledges receipt of your facility's response, dated February 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 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 investigator noted that drug products produced by your firm failed to meet the conditions of section 503A. For example, the investigator noted that 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 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, the investigator noted:

1. An operator donning a non-sterile coverall suit after it touched the floor in the ISO 8 anteroom for use in the ISO 5 aseptic processing area.

2. Your firm failed to depyrogenate your in-process glassware before use in aseptic drug production.

3. Your firm had no evidence to demonstrate that media fill studies were conducted.

4. Your firm failed to demonstrate through appropriate studies that your hood is able to provide adequate protection of the ISO 5 area in which sterile products are produced. 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 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 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 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)).

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

4. Your firm failed to clean and, where indicated by the nature of the drug, sterilize and process container closures to remove pyrogenic properties to assure they are suitable for their intended use (21 CFR 211.94(c)).

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

6. 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)).

It is a prohibited act under section 301(k) of the FDCA [21 U.S.C. § 331(k)] to perform 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 your response related to the insanitary conditions cited above, we are unable to fully evaluate the following corrective action due to a lack of adequate supporting documentation. Specifically, in response to our observation concerning

media fills, you stated, “Process simulation tests (media fills) are being performed **(b)(4)**.” However, your response only included a log of incubation results from your media fills. Therefore, we are unable to determine if your media fills closely simulate aseptic production operations.

Furthermore, the following corrective actions appear inadequate to address the insanitary conditions noted above:

1. Your smoke studies were not performed under dynamic conditions. Specifically, the video provided in your response did not simulate routine production, including the use of production equipment. Conducting smoke studies under dynamic conditions helps to ensure that unidirectional airflow is maintained while personnel are working in the ISO 5 area.

2. Your firm’s **(b)(4)** temperature and time cycle is not adequate to depyrogenate glassware. The use of non-depyrogenated equipment can introduce or increase endotoxins in the finished drug product.

For more information on compounding, please see FDA’s website, at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm.

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.[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 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: Tina M. Pawlowski, Ph.D., Compliance Officer
U. S. Food and Drug Administration
Division of Pharmaceutical Quality Operations III

Refer to the Unique Identification Number (Case# 536189) when replying. If you have questions regarding the contents of this letter, please contact Dr. Pawlowski by phone at (313) 393-8217.

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

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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.