US Specialty Formulations LLC 9/30/16

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Philadelphia District
US Customs House, Room 900
200 Chestnut Street
Philadelphia, PA 19106
Telephone: (215) 597-4390
FAX: (215) 597-0875

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER
16-PHI-15

September 30, 2016

Kyle Y. Flanigan, PhD
Chief Executive Officer
US Specialty Formulations, LLC
116 Research Drive
Bethlehem, PA 18015-4731

Dear Dr. Flanigan:

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 January 31, 2014, and again on November 28, 2014, and December 24, 2015. From May 11, 2015, to May 29, 2015, FDA investigators inspected your facility, US Specialty Formulations, LLC, located at 116 Research Drive, Bethlehem, PA 18015-4731. During the inspection, the investigators observed that your firm did not have an adequate contact time for your sporicidal agent used to disinfect your aseptic processing areas. Specifically, the 30 seconds contact time for Actril appears to be inadequate for sporicidal effect. In addition, your firm's environmental program did not include personnel monitoring sampling. Also, our investigators noted that your operators donned their gowning in an unclassified office area.

In addition, the investigators observed that you failed to meet the conditions under section 503B of the FDCA necessary for drugs produced by an outsourcing facility to qualify for

exemptions from certain requirements under the FDCA. FDA issued a Form FDA 483 to your facility on May 29, 2015. FDA acknowledges receipt of your facility's response, dated June 11, 2015.

Based on this inspection, it appears your facility is producing drugs that violate the FDCA.

A. Compounded Drugs under the FDCA

The Drug Quality and Security Act (DQSA) was enacted on November 27, 2013. Title I of the DQSA, the Compounding Quality Act (CQA), added a new section 503B to the FDCA. Under section 503B(b), 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 can 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.

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 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.

B. Violations of the FDCA

The FDA investigators noted that drug products that were intended or expected to be sterile were prepared, packed, or held under insanitary conditions whereby they may have been contaminated with filth or rendered injurious to health, causing them to be adulterated within the meaning of section 501(a)(2)(A) of the FDCA. Furthermore, the FDA investigators observed significant CGMP violations at your facility, causing your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA.

In addition, the FDA investigators observed that your facility failed to meet the conditions of section 503B. For example, during the inspection, FDA investigators noted that some of your facility's drug products do not include the following on the label:

1. "This is a compounded drug;"
2. the name, address and phone number of the outsourcing facility;
3. the dosage form and strength of the drug;
4. the statement of the quantity or volume, as appropriate;
5. storage and handling instructions (your preservative-free products are not described as single-dose containers); and
6. a list of the inactive ingredients, identified by established name and the quantity or proportion of each ingredient [section 503B(a)(10) of the FDCA [21 U.S.C. §353b(a)(10)(A)]].

Additionally, some of your drugs do not include information on the container to facilitate adverse event reporting [section 503B(a)(10)(B) of the FDCA [21 U.S.C. §353b(a)(10)(B)]].

Your facility also failed to submit a report to FDA upon registering as an outsourcing facility in January 2014, identifying the drug products that you compounded during the previous 6-month period [section 503B(b)(2) of the FDCA [21 U.S.C. §353b(b)(2)]].

Because your compounded drug products have not met all of the conditions in section 503B, they are not eligible for the exemptions under section 503B from the FDA approval requirements in 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.[2]

Specific violations are described below.

Adulterated Drug Products

FDA investigators noted that drug products compounded in your facility that were 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 your firm did not have an adequate contact time for your sporicidal agent used to disinfect your aseptic processing areas. Specifically, the 30 seconds contact time for Actril appears to be inadequate for sporicidal effect. In addition, your firm's environmental program did not include personnel monitoring sampling. Also, our investigators noted that your operators donned their gowning in an unclassified office area.

FDA investigators also noted CGMP violations at your facility, causing 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 an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions. [21 CFR211.42(c)(10)(v)]

2. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas. [21CFR211.42(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 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]

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

6. Your firm does not have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. [21 CFR 211.165(a)]

7. Your firm failed to ensure that each batch of drug product purporting to be sterile and pyrogen-free is laboratory tested to determine conformance to such requirements prior to release. [21 CFR 211.167(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 draft guidance, *Current Good Manufacturing Practice — Interim 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.

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 your drug products.[3] Under sections 301(d) and 505(a) of the FDCA [21 U.S.C. §§ 331(d) and 355(a)], a new drug may not be introduced 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.

Misbranded Drug Products

You compound drug products that are intended for conditions that are 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, and they are not exempt from the requirements of section 502(f)(1) of the FDCA (*see, e.g.,* 21 CFR 201.115). The introduction or delivery for introduction into interstate commerce of these products therefore violates section 301(a) of the FDCA. Further, 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 January 2014 identifying the drug products that you compounded during the previous 6-month period. (Section 503B(b)(2) of the FDCA [21 U.S.C. § 353b(b)(2)]). 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)].

C. Corrective Actions

FDA acknowledges your response to the Form FDA 483 dated June 11, 2015. In that submission you indicated that your firm is reviewing its labels to ensure compliance; however, no label samples were included with your response. In addition, during the inspection, FDA investigators noted that your facility did not have a licensed pharmacist present during production of sterile drug products. In your May 14, 2015, letter to FDA, which was incorrectly dated March 14, 2015, your firm committed to have a pharmacist physically present during sterile production as of May 21, 2015. Note that FDA intends to provide

guidance on what it means for a drug product to be compounded by or under the direct supervision of a licensed pharmacist and intends to provide answers and additional guidance publicly.

Furthermore, your response to the Form FDA 483 described corrective actions you have implemented or will be implementing to address deficiencies observed at your facility during the inspection. Although the proposed actions appear to correct some deficiencies, the adequacy of these corrective actions cannot be fully evaluated due to lack of supporting documentation. For example, your firm initiated multiple CAPA (corrective and preventive action) reports to describe and document the implementation of the changes to your standard operation procedures and processes. However, no CAPA report was included in the response to evaluate the adequacy of the changes, timeframes, and implementation. In addition, your firm revised multiple SOPs, such as the cleaning and disinfecting and the batch production record SOPs. However, your response did not include the revised procedures, nor did it include training records to support adequate implementation of the changes. Moreover, your response does not address any interim actions to be put into place prior to the full implementation of corrective actions.

In addition, other proposed actions appear to be inadequate. For example, we remain concerned with the averaging of testing assay results and the claim that individual replicates test results are not required to meet specifications. Also, regarding the revised procedure for visual inspection, it is unclear what actions your firm will take if the established reject limits are exceeded.

FDA strongly recommends that your management immediately undertake a comprehensive assessment of your operations, including facility design, procedures, personnel, processes, materials, and systems. In particular, this review should assess your aseptic processing operations. A third party consultant with relevant sterile drug manufacturing expertise could be useful in conducting this comprehensive evaluation. You should fully implement necessary corrections in order to ensure that the drug products produced by your firm conform to the basic quality standards that ensure safety, identity, strength, quality, and purity.

D. 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. FDA intends to re-inspect your facility to verify corrective actions have been completed.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps 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 the corrective actions cannot be completed within fifteen working days, state the reason for the delay and the time frame within which the corrections will be completed. Your written notification should refer to the Warning Letter Number above 16-PHI-15. Please address your response to:

Yvette Johnson, Compliance Officer
FDA Philadelphia District Office
U.S. Food and Drug Administration
Room 900, US Customhouse
2nd & Chestnut Streets
Philadelphia, PA 19106

If you have questions regarding any issues in this letter, please contact Ms. Johnson via email at Yvette.Johnson@fda.hhs.gov or by phone at 215-717-3077.

Sincerely,
/S/
Anne E. Johnson
Philadelphia District Director

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[1] *See* Pub. L. No. 113-54, § 102(a), 127 Stat. 587, 587-588 (2013).

[2] *See, e.g.,* section 503B(a)(11) of the FDCA [21 U.S.C. § 353b(a)(11)].

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