Triangle Compounding 11/2/15

Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Atlanta District
60 Eighth Street NE
Atlanta, GA 30309

November 2, 2015

VIA UNITED PARCEL SERVICE

WARNING LETTER
(16-ATL-02)

Danny Barnes, President
Triangle Compounding Pharmacy
3700 Regency Pkwy, Suite 140
Cary, NC 27518-8696

Dear Mr. Barnes:

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 24, 2014. From September 8, 2014, to September 22, 2014, and from January 12, 2015, to January 16, 2015, FDA investigators inspected your facility, Triangle Compounding Pharmacy, 3700 Regency Parkway, Suite 140, Cary, NC. These were the first inspections that evaluated your facility as an outsourcing facility under the requirements of section 503B. The September 2014 was an initial inspection of your 503B facility as well as an investigation into adverse events reported after the use of sterile drug products produced by your facility. The January 2015 inspection was a reinspection to determine whether compliance had been achieved after the September inspection, to obtain further information regarding sterility failures and complaints, and to collect sterile drug product samples for testing. 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 September 22, 2014, and a second one on January 16, 2015. FDA acknowledges receipt of your firm's responses, dated October 10, 2014, February 5, 2015, and May 29, 2015.

Based on these inspections, 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 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, FDA investigators observed that your facility failed to meet the conditions of section 503B. For example, during the inspection, FDA investigators noted that your facility 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. Furthermore, the reports submitted on July 3, 2014, and December 31, 2014, failed to identify all drugs compounded at your facility (section 503B(b)(2) of the FDCA [21 U.S.C. §353b(b)(2)]).

Furthermore, to qualify for the exemptions under section 503B, an outsourcing facility may not compound drugs that appear on a list of drugs developed by the Secretary that have been withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective (section 503B(a)(4) of the FDCA [21 U.S.C § 353b(a)(4)]). This list of drugs appears at 21 CFR 216.24 and includes chlorhexidine gluconate. The product report you submitted June 26, 2015, includes three products formulated with chlorhexidine gluconate. Although we do not have specific information regarding the formulation(s) or intended use(s) of your chlorhexidine gluconate products, all tinctures of chlorhexidine

gluconate formulated for use as a patient preoperative skin preparation are included on the list published by FDA at 21 CFR 216.24.

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 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 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 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).
2. Your firm failed to establish adequate written procedures designed to assure batch uniformity and integrity of drug products that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch (21 CFR 211.110(a)).
3. Your firm failed to ensure container closure systems provide protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product (21 CFR 211.94(b)).
4. 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)).

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.

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

Because your compounded drug products have not met all of the conditions in section 503B, they are not eligible for the exemption under section 503B from the requirement under section 502(f)(1) that labeling bear adequate directions for use. 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, and adequate directions cannot be written for them 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). 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. Furthermore, the reports submitted on July 3, 2014, and December 31, 2014, failed to identify all drugs compounded at your facility. (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

In your response to the Form FDA 483 inspectional observations dated February 5, 2015, you describe certain corrective actions taken to address the observations. Although several of your proposed corrective actions appear adequate, others are deficient. For example, in your response to our observation regarding the stability of stock solutions, it is not clear whether or not your firm will conduct a similar testing study for assay, endotoxin, particulate matter, and sterility for all stock solutions aside from the specific examples listed in your response. We acknowledge that your additional correspondence dated May 29, 2015, includes sterility testing results at **(b)(4)** for the Morphine Sulfate stock solution; however, no sterility data at the expiry period was provided for the other stock solutions.

In addition, in response to our observation regarding deficient cleaning, your firm updated dwell times of some disinfectants; however, you did not provide sufficient information to justify the dwell time of sterile **(b)(4)**. Furthermore, you provided insufficient documentation to show that all disinfectants used within the ISO 5 hood are sterile.

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-ATL-02). Please address your reply to Marie Mathews, at the address above.

If you have questions regarding the contents of this letter, please contact Marie Mathews at (404) 253-1279.

Sincerely,
/S/
Ingrid A. Zambrana
Atlanta 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)].