Cantrell Drug Company 1/21/15

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Dallas District
4040 North Central
Expressway
Dallas, Texas 75204-3128

January 21, 2015

UPS OVERNIGHT

2015-DAL-WL-12

WARNING LETTER

James L. McCarley Jr., CEO
Michael W. Pierce, President
Cantrell Drug Company
7321 Cantrell Rd
Little Rock, AR 72207-4144

Dear Messrs. McCarley and Pierce:

Between October 15, 2013 and November 4, 2013, U.S. Food and Drug Administration (FDA) investigators conducted an inspection of your facility, Cantrell Drug Company, located at 7321 Cantrell Rd, Little Rock, AR 72207-4144. The investigators observed serious deficiencies in your practices for producing sterile drug products, which put patients at risk. For example, our investigators observed that your firm failed to demonstrate through appropriate studies that your hoods are 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. A Form FDA-483 was issued to your firm on November 4, 2013.

Based on this inspection, it appears that you are producing drugs that violate the Federal Food, Drug, and Cosmetic Act (FDCA).

FDA acknowledges that Cantrell registered its facility with FDA as a 503B outsourcing facility on December 16, 2013.

A. Compounded Drugs Under the FDCA

At the time FDA inspected your facility, there were conflicting judicial decisions regarding the applicability of section 503A of the FDCA [21 U.S.C. § 353a], which exempts compounded drugs from several key statutory requirements if certain conditions are met.[1] Nevertheless, receipt of valid prescriptions for individually-identified patients prior to distribution of compounded drugs was relevant for both section 503A of the FDCA and the agency's Compliance Policy Guide 460.200 (CPG) (2002), which was then in effect.[2] During the FDA inspection, the investigators observed that your firm does not receive valid prescriptions for

individually-identified patients for a portion of the drug products you produce. Based on this factor alone, those drugs were not entitled to the statutory exemptions for compounded drugs described in section 503A of the FDCA and did not qualify for the agency's exercise of enforcement discretion set forth in the CPG.[3]

Since FDA inspected your facility, Congress enacted and the President signed into law the Compounding Quality Act (CQA),[4] which amended FDCA section 503A by eliminating the advertising restrictions that had been the basis for conflicting judicial decisions. The CQA otherwise left section 503A intact, and so clarified that the remainder of section 503A, including the requirement of valid prescriptions for individually-identified patients, is applicable in every federal judicial circuit.

The CQA adds a new section 503B to the FDCA [21 U.S.C. § 353b].[5] Under section 503B(b), a compounder can register as an outsourcing facility with FDA.[6] As noted previously, Cantrell registered the facility referenced in this letter with FDA as a section 503B outsourcing facility on December 16, 2013. Drug products compounded in a registered outsourcing facility can qualify for exemptions from the FDA approval requirements in section 505 of the FDCA [21 U.S.C. § 355(a)] and the requirement to label products with adequate directions for use under section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)] if the drug is compounded by or under the direct supervision of a licensed pharmacist and the conditions in section 503B are met. An outsourcing facility compounding under section 503B may or may not obtain prescriptions for individually-identified patients.

To qualify for the exemptions under section 503B, the drug products must be compounded in an outsourcing facility that meets all of the conditions set forth in section 503B of the FDCA, which include, but are not limited to, submitting adverse event reports and labeling compounded products with certain information. In addition, 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 compliance with 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 finished drug products are established in Title 21 of the Code of Federal Regulations (CFR) parts 210 and 211.

B. Violations of the FDCA

The drug products that you manufactured and distributed without valid prescriptions for individually-identified patients before you registered as an outsourcing facility were not the subject of approved applications, and they are therefore unapproved new drugs in violation of section 505(a) of the FDCA. In addition, because these products were intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners, adequate directions could not be written for them so that a layman could 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. Finally, the manufacture of those drugs was also subject to FDA's CGMP regulations for Finished Pharmaceuticals, Title 21 CFR parts 210 and 211. FDA investigators observed significant CGMP violations at your facility, causing such drug product(s) to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA.

Because your facility is now registered under section 503B as an outsourcing facility, this letter focuses on the observed CGMP violations. CGMP requirements continue to apply now that you have registered your facility as an outsourcing facility.

CGMP Violations Observed During FDA's Inspection

FDA investigators observed CGMP violations at your facility, causing the drug products for which you did not obtain valid prescriptions for individually-identified patients to be adulterated under section 501(a)(2)(B) of the FDCA. The violations observed at your facility include, 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 monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

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)).

Before you registered as an outsourcing facility, the CGMP violations described above applied only to the drug products for which you did not obtain valid prescriptions for individually-identified patients. Now that you are an outsourcing facility, all of your drugs must be made in accordance 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 also 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 during this interim period.

C. Corrective Actions

In your response dated November 21, 2013, to the Form FDA 483, you described certain corrective actions you took in response to the Form FDA 483 observations. You also indicated that you adhere to USP Chapter <797> "Pharmaceutical Compounding – Sterile Preparations." Since providing these responses, you subsequently registered as an outsourcing facility, and are subject to CGMP requirements under the new law.

Although several of your proposed corrective actions appear adequate, others are deficient. For example, your media fill studies do not closely simulate aseptic manufacturing operations incorporating, as appropriate, worst-case activities and challenging conditions. An approach that only focuses on the risk posed by the **(b)(4)**. Furthermore, in manually intensive filling processes, a large number of units, generally approaching the full production batch size, should be used.

Regarding the validation of the **(b)(4)** sterilization processes, a **(b)(4)** is required to provide an adequate level of sterility assurance.

You indicate that you follow USP Chapter <797> "Pharmaceutical Compounding – Sterile Preparations" regarding gowning practices, be advised that as a registered outsourcing facility, you must adhere to CGMP requirements. Therefore, only appropriately gowned personnel should be permitted access to the aseptic manufacturing areas.

Furthermore, your firm relies upon an alternative test method to USP <71> "Sterility Tests" to conduct sterility testing. Your firm should consult USP <1223> "Validation of Alternative

Microbiological Methods" for further guidance. Alternative methods may be used if they are appropriately validated and shown to be adequate for their intended use.

Your firm's planned corrections do not meet the minimum requirements of 21 CFR parts 210 and 211, and there is no assurance that the drug products produced by your firm conform to the basic quality standards that ensure safety, identity, strength, quality, and purity.

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.

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 assure that your firm complies with all requirements of federal law and 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 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 be addressed to:

Jeff R. Wooley, Compliance Officer
FDA Dallas District Office
U.S. Food and Drug Administration
4040 North Central Expressway
Suite 300
Dallas, TX 75204-3158

If you have questions regarding any issues in this letter, please contact our office at 214-253-5251.

Sincerely,
/S/
Reynaldo R. Rodriguez, Jr.
Dallas District Director

Cc: John Clay Kirtley, Pharm.D.
Executive Director
Arkansas State Board of Pharmacy
322 South Main Street, Suite 600
Little Rock, AR 72201

[1] *Compare Western States Med. Ctr. v. Shalala*, 238 F.3d 1090 (9th Cir. 2001) *with Medical Ctr. Pharm. v. Mukasey*, 536 F.3d 383 (5th Cir. 2008).

[2] The CPG set forth a non-exhaustive list of factors that FDA considered in determining whether to take enforcement action when the scope and nature of a pharmacy's activities raised concerns. This CPG has been withdrawn in light of new legislation. See below.

[3] *See* 21 U.S.C. § 353a(a) (granting compounded drugs statutory exemptions if, among other things, "the drug product is compounded for an identified individual patient based on the . . . receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient . . . ."); CPG at 2 ("FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of human drugs upon receipt of a valid prescription for an individually-identified patient from a licensed practitioner. This traditional activity is not the subject of this guidance.").

[4] Drug Quality and Security Act, Public Law 113-54, 127 Stat. 587 (Nov. 27, 2013).

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

[6] *See* Draft Guidance for Industry, "Registration for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act," (December, 2013).