Brookfield Medical/Surgical Supply, Inc. 7/5/16

Department of Health and Human Services

Public Health Service
Food and Drug Administration
New England District Office
One Montvale Avenue, 4th floor
Stoneham, MA 02180
Phone 781.587.7500
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WARNING LETTER
CMS # 492682

UNITED PARCEL SERVICE
OVERNIGHT DELIVERY

July 5, 2016

James P. Cangelosi, R.Ph., President/Owner
Brookfield Medical/Surgical Supply, Inc.
60 Old New Milford Road, Suite 1B
Brookfield, CT 06804-2430

Dear Mr. Cangelosi:

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 12, 2015. From March 30, 2015, to April 9, 2015, an FDA investigator inspected your facility, Brookfield Medical/Surgical Supply, Inc., located at 60 Old New Milford Road, Suite 1B, Brookfield, CT 06804-2430. During the inspection, the investigator observed serious deficiencies in your practices for producing sterile drug products, which put patients at risk. For example, the investigator observed yellowing borders and bleeding into a HEPA filter in your ISO 7 area, peeling paint on the ceiling of your ISO 8 area, and uncovered spiral fluorescent light bulbs that are not easy to clean in your ISO 5 hood. In addition, your firm does not use a sporicidal agent as part of the disinfection program for the ISO 5 hood and ISO 7 cleanroom where sterile drug products are prepared. Furthermore, your firm failed to demonstrate through appropriate studies that the aseptic processing areas 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.

In addition, the investigator 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 April 9, 2015. FDA acknowledges receipt of your facility's responses, dated April 29, 2015, and December 7, 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 investigator 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 investigator 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 investigator observed that your facility failed to meet the conditions of section 503B. For example, during the inspection, the FDA investigator noted that some of your facility's drug products do not include the following on their label: the statement, "This is a compounded drug" and your facility's phone number. Furthermore, the container for some drug products you produce do not

include the following: Information to facilitate adverse event reporting: www.fda.gov/medwatch and 1–800–FDA–1088, and directions for use, including, as appropriate, dosage and administration. [Section 503B(a)(10) of the FDCA [21 U.S.C. §353b(a)(10)]].

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

The FDA investigator 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 investigator observed yellowing borders and bleeding into a HEPA filter in your ISO 7 area, peeling paint on the ceiling of your ISO 8 area and uncovered spiral fluorescent light bulbs that are not easy to clean in your ISO 5 hood. In addition, your firm does not use sporicidal agent as part of the disinfection program for the ISO 5 hood and ISO 7 cleanroom where sterile drug products are prepared. Furthermore, your firm failed to demonstrate through appropriate studies that the aseptic processing areas 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.

The FDA investigator 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 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 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 maintain buildings used in the manufacture, processing, packing or holding of drug products in a clean and sanitary condition. (21 CFR 211.56(a))

5. Your firm failed to establish time limits for the completion of each phase of production to assure the quality of the drug product. (21 CFR 211.111)

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

7. 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))

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).

Further, you compound drug products with labeling that states only that the products are "for Injection," and do not include appropriate directions for, or limitations to, the proper administration of those products. Specifically, the product labels do not include the warning that such products should not be administered intravenously. Improper injection of your products could lead to serious adverse

events. Consequently, their labeling fails to bear such adequate warnings against unsafe dosage or methods or durations of administration or application, in such manner and form, as are necessary for the protection of users, causing them to be misbranded under section 502(f)(2) of the FDCA. Furthermore, the products, when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling, are dangerous to health, causing them to be misbranded under section 502(j) of the FDCA.

The introduction or delivery for introduction into interstate commerce of such 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

C. Corrective Actions

In your April 29, 2015, and December 7, 2015, responses, you described certain corrective actions you planned to take in response to the Form FDA 483 observations. However, FDA is unable to evaluate your proposed corrective actions because of a lack of supporting documentation. For example, your response states that you will implement use of a sporicidal agent, but it did not identify the sporicidal agent or when the changes will be effective. In addition, you did not provide documentation of the noted repairs and of the cleaning of the ISO 5, ISO 7 and ISO 8 areas. Also, you did not provide your SOP and training documentation, regarding not turning off the ISO 5 **(b)(4)** each day. FDA intends to verify the implementation and adequacy of your firm's planned corrective actions during FDA's next inspection.

In addition, your response indicated that because your firm only sells products to physicians' offices, hospitals and surgery centers, directions for use would be determined by the physician. However, one of the conditions of section 503B is that the outsourcing facility must include specific information in the labeling of the drug products it produces, including "directions for use, including, as appropriate, dosage and administration." See section 503B(a)(10)(B)(iii) of the FDCA. Some of your product labels and containers are inadequate, as they state only that your products are "for Injection," and do not include directions for use, including, as appropriate, dosage and administration for your products. Improper injection of your products could lead to serious adverse events.

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 product(s) produced by your firm conform to the basic quality standards that ensure safety, identity, strength, quality, and purity.

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, as amended by the Food and

Drug Administration Safety and Innovation Act (Pub.L. 112-144, Title VII, section 711). We note that you have chosen to hire a contract testing laboratory to perform some of the required testing of your finished drug products. 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 introduce into interstate commerce are neither adulterated nor misbranded. [*See* 21 CFR 210.1(b), 21 CFR 200.10(b)].

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 (CMS# 492682). Please address your reply to Compliance Officer Rory Geyer, at the address above.

If you have questions regarding the contents of this letter, please contact Compliance Officer Rory Geyer at 781-587-7521 or rory.geyer@fda.hhs.gov.

Sincerely,
/S/
Joseph Matrisciano, Jr.
District Director
New England District

[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.