SSM Health Care St. Louis DBA SSM St. Clare Health Center 10/19/15

Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Southwest Region
Kansas City District
8050 Marshall Drive
Suite 205
Lenexa, Kansas 66214-152
913-495-5100

October 19, 2015

Via UPS

WARNING LETTER
Ref. CMS# 456683

Kristina N. Bryowsky, PharmD, BCPS, Director Pharmacy
SSM Health Care St. Louis dba SSM St. Clare Health Center
1015 Bowles Avenue
Fenton, MO 63026

Dear Ms. Bryowsky:

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 February 18, 2014, and again on January 5, 2015. From August 4, 2014, to August 14, 2014, an FDA investigator inspected your facility, SSM Health Care St. Louis, dba SSM St. Clare Health Center, located at 1015 Bowles Avenue, Fenton, MO 63026. 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 an operator dropping an IV bag on the floor and using it after spraying it with sterile **(b)(4)**. In addition, the investigator observed that 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. 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 August 14, 2014. FDA acknowledges receipt of your facility's response, dated August 22, 2014.

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.

The FDA investigator also observed that your facility failed to meet the conditions of section 503B. For example, during the inspection, an FDA investigator noted that the majority of your facility's drug products:

1. Do not include the following on the label: the dosage form; the date the drug was compounded; and storage and handling instructions;
2. Do not list the active and inactive ingredients, identified by established name and the quantity or proportion of each ingredient, on the drug product label or the container;
3. Do not contain all of the required information to facilitate adverse event reporting on the container.

[Section 503B(a)(10) of the FDCA [21 U.S.C. §353b(a)(10)]].

In addition, your facility failed to submit a report to FDA upon initial registration as an outsourcing facility in February 2014, and in June and December of 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

An 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 an operator dropping an IV bag on the floor and using it In addition, 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.

An FDA investigator also noted CGMP violations at your facility, causing your drug products 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 ensure that manufacturing personnel wear clothing appropriate to protect drug product from contamination (21 CFR 211.28(a)).
2. 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)).
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 has failed to prepare batch production and control records with complete information relating to production and control of each batch of drug product (21 CFR § 211.188).
5. Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed (21 CFR § 211.192).

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 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

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 such 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 February 2014, and again in June 2014 and December 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

Your August 22, 2014, response to issues identified in our Form FDA 483 describes corrective actions you took or intend to take. The district also held a telephone conference with your firm following the inspection regarding your response to failing assay results and stability test results. Some of your proposed corrective actions appear to be adequate, but others remain deficient or cannot be evaluated because of a lack of supporting documentation. For example, in response to Form FDA 483 Observation 10 ("The labels of your outsourcing facility's compounded drug products do not include information required in section 503B(a)(10)(A)"), you state that, "[i]mmediately upon notification of the concern, the label was modified to contain all the elements required" in section 503B(a)(10)(A), with a photograph of a label appearing immediately below, presumably to demonstrate the corrections implemented. However, the label depicted in your response remains deficient as it fails to include the following information required by section 503B(a)(10)(A): the date the drug was compounded; the dosage form; and storage and handling instructions. Moreover, your response did not address any corrections made regarding the container deficiency noted in Observation 10 ("[Y]our outsourcing facility's drug product container labels do not contain the following information to

facilitate adverse event reports: www.fda.gov/medwatch and 1-800-FDA-1088”). While the label depicted in your response references the MedWatch website, container labels for drug products compounded under section 503B must also provide the MedWatch phone number.

In addition, your firm did not provide a standard operating procedure (SOP) that provided adequate instructions for performing dynamic smoke studies and evidence that the smoke studies conducted on **(b)(4)**, were conducted under dynamic conditions, making us unable to assess the adequacy of your response to Form FDA 483 Observation 4.

The Conduct of Personnel and Overview of Aseptic Technique section of your Pharmacy Policy is deficient because it allows use of medications that have fallen on the floor, which poses an unacceptable risk of drug product contamination and which should be ceased.

There is a lack of data to support the established beyond use date (BUD) for Nicardipine and Oxytocin, making us unable to assess the adequacy of your response to this issue. You also failed to conduct adequate investigations when assay results failed to meet acceptance testing.

The detailed checklist that was put in place to document each critical step, in response to Form FDA 483 Observation 7, does not match the master batch records for each compounded drug product. In addition, your firm does not record the actual components used on the checklist (e.g., **(b)(4)**).

During a review of your Pharmacy Policy we determined that the media fill section appears to be deficient. For example, you use **(b)(4)** for low and medium risk levels which does not represent your actual manufacturing practices of **(b)(4)**. The media fill section of your Pharmacy Policy should be revised to simulate your actual manufacturing practices.

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.

In addition to the issues discussed above, we 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). 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 (Ref. CMS# 456683). Please address your reply to Danial S. Hutchison, at the address above.
If you have questions regarding the contents of this letter, please contact Danial S. Hutchison at 913-495-5154.

Sincerely,
/S/
Cheryl. A. Bigham
Kansas City District Director

---

[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)].