Pharmakon Pharmaceuticals 5/21/15

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Detroit District
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Telephone: 313-393-8100
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WARNING LETTER
2015-DET-12

VIA UPS

May 21, 2015

Paul J. Elmer, President
Pharmakon Pharmaceuticals
14450 Getz Road
Noblesville, IN 46060-3303

Dear Mr. Elmer:

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 23, 2014, and again on December 2, 2014. From March 5, 2014, to March 13, 2014, FDA investigators inspected your facility, Pharmakon Pharmaceuticals, located at 14450 Getz Road, Noblesville, IN 46060-3303. FDA again inspected your facility from April 2, 2014, to April 8, 2014, after receiving reports of adverse events (over-sedation) in neonatal infants who were

administered midazolam that you labeled with an incorrect concentration.

During the inspections, the investigators observed serious deficiencies in your practices for producing sterile drug products, which put patients at risk. For example, the investigators observed technicians touching non-sterile surfaces with gloved hands and then performing aseptic manipulations without first re-disinfecting gloves. Furthermore, the investigators found 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. 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 Form FDA 483s to your firm on March 13, 2014, and on April 8, 2014. FDA acknowledges receipt of your facility's responses, dated March 28, 2014, and April 23, 2014. FDA also acknowledges your actions in March 2014 and in April 2014 to voluntarily recall lots of Midazolam in 0.9% Sodium Chloride and Atropine Sulfate drug products that were improperly labeled. 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 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, 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. You also produced a drug the name of which is recognized in an official compendium, the United States Pharmacopeia (USP), and the strength of the drug fell below the standards set forth in this compendium, causing it to be adulterated within the meaning of section 501(b) of the FDCA [21 U.S.C. § 351(b)].

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:

1. Some of your facility's drug products do not include the following information on the labeling: address and phone number of your facility, the dosage form of the drug product, and the statement, "This is a compounded drug." In addition, some of your products do not list the inactive ingredients on the drug product label nor on the container label. (Section 503B(a)(10) of the FDCA [21 U.S.C. §353b(a)(10)]).

2. Your facility failed to submit a report to FDA upon initial registration as an outsourcing facility in January 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)]).

Because your compounded drug products have not met all of the conditions in section 503B of the FDCA, 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] Mislabeled drug products that you distributed and subsequently recalled are also misbranded under sections 502(a), 502(f)(2), and 502(j) of the FDCA [21 U.S.C. 352(a), 352(f)(2), and 352(j)].

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 technicians touching non-sterile surfaces with gloved hands and then performing aseptic manipulations without first re-disinfecting gloves. Furthermore, the investigators found 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

In addition, FDA received a MedWatch report on March 28, 2014 indicating issues with two of your batches of midazolam injection. The two batches were labeled 0.2 mg midazolam/2mL in 0.9% Sodium Chloride. FDA analysis of two samples from each of the two lots found that they contained 187.3% and 180.4% of the declared concentration. Under section 501(b) of the FDCA, a drug is adulterated if it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium. The strength of your midazolam injection product did not comply with standards set forth in the official USP Midazolam Injection monograph, which defines a Midazolam injection as having no less than 90% and no more than 110% of the labeled amount of Midazolam, causing it to be adulterated under section 501(b) of the FDCA.

FDA investigators 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 carefully examine labeling materials issued for a batch for identity and conformity to the labeling specified in the batch production records (21 CFR 211.125(b)).
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 maintaining equipment used to control the aseptic conditions (21 CFR 211.42(c)(10)(vi)).
4. Your firm failed to ensure that manufacturing personnel wear clothing appropriate to protect drug product from contamination (21 CFR 211.28(a)).
5. 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)).
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, 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).

In addition, in March 2014, you voluntarily recalled two lots of Midazolam 0.2 mg/2mL in 0.9% Sodium Chloride that contained nearly twice the labeled strength of midazolam. Under section 502(a) of the FDCA, a drug product is misbranded if its labeling is false or misleading in any particular. Because the labeling of these drug products was false, they are misbranded under section 502(a) of the FDCA.

In April 2014, you voluntarily recalled two lots Midazolam HCl 1 mg/ml in 0.9%

Sodium Chloride, one lot of Midazolam HCl 2mg/mL in 0.9% Sodium Chloride, and one lot of Atropine Sulfate 0.4 mg/mL, which did not contain the warning, "Contains Benzyl Alcohol." The labeling of these drug products is false because it did not declare that the drug products contained benzyl alcohol, causing them to be misbranded under section 502(a) of the FDCA. Furthermore, under section 502(f)(2) of the FDCA, a drug product is misbranded if its labeling does not contain such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health. As FDA indicated in a letter to you dated August 25, 2014, these drug products could be used in neonates, and the use of benzyl alcohol puts neonatal intensive care unit patients at risk of life-threatening adverse events. No concentration of benzyl alcohol is safe in the neo-natal population. Therefore, these products are misbranded under section 502(f)(2) of the FDCA.

As FDA indicated in letters to your firm dated June 9, 2014, and August 25, 2014, the improperly labeled products represented a serious health hazard, which may be life-threatening. Because of the health hazard, FDA classified both of these actions as Class I recalls. Under section 502(j) of the FDCA, a drug product is misbranded if it is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested, in the labeling thereof. The midazolam HCl and atropine sulfate drug products subject to your March 2014 and April 2014 recalls are therefore misbranded under section 502(j) of the FDCA.

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 misbranded is a prohibited act. 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, 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

In your March 28, 2014 and April 23, 2014 responses to the Form FDA 483s issued at the close of FDA's inspections of your facility, you described certain corrective actions you took in response to the Form FDA 483 observations. Although several of

your proposed corrective actions appear adequate, others are deficient. For example, for many of the new or revised procedures, you did not indicate implementation dates nor have you provided training records. In addition, you did not provide any documentation to demonstrate that you have successfully implemented the corrective actions, such as invoices showing any newly purchased equipment and supplies related to corrective actions or validation reports.

FDA strongly recommends that your management immediately undertake a comprehensive assessment of your operations, including facility design, procedures, personnel, processes, materials, systems, and labeling. 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. Please address your reply to:

Tina M. Pawlowski, Ph.D., Compliance Officer
FDA Detroit District Office
U.S. Food and Drug Administration
300 River Place, Suite 5900
Detroit, MI 48207

If you have questions regarding any issues in this letter, please contact Compliance Officer Pawlowski at 313-393-8217 or by email at tina.pawlowski@fda.hhs.gov.

Sincerely,
/S/
Art O. Czabanuik
District Director
Detroit District Office

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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.

More in 2015

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