Central Admixture Pharmacy Services, Inc. 8/19/16

Department of Health and Human Services

Public Health Service
Food and Drug Administration
PHILADELPHIA DISTRICT
900 U.S. Customhouse
2nd and Chestnut Streets
Philadelphia, PA 19106
Telephone: 215-597-4390

WARNING LETTER
16-PHI-11
August 19, 2016

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Thomas J. Wilverding, President
Central Admixture Pharmacy Services, Inc.
6580 Snowdrift Road, Suite 100
Allentown, PA 18106-9331

Dear Mr. Wilverding:

You registered two facilities, located in Allentown, Pennsylvania and San Diego, California, with the U.S. Food and Drug Administration (FDA) as outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act (FDCA) [21 U.S.C. § 353b][1] on February 28, 2014 and June 4, 2014, respectively, and both facilities on December 23, 2015.

From June 4, 2014, to June 11, 2014, and from February 3, 2015, to February 11, 2015, FDA investigators inspected your facility located at 6580 Snowdrift Road, Suite 100, Allentown, PA (Allentown facility). From August 4, 2014, to August 8, 2014, FDA investigators inspected your facility located at 7935 Dunbrook Road, Suite C, San Diego, CA (San Diego facility).

During the inspections, the investigators observed serious deficiencies in your practices for producing sterile drug products at both the Allentown facility and San Diego facility, which put patients at risk. For example, at the Allentown facility,

investigators observed that procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written, and followed. At the San Diego facility, investigators observed that testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the final specifications prior to release, and procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written, and followed. Therefore, at both facilities, your products may be produced in an environment that poses a significant contamination risk. In addition, investigators at both facilities 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 Allentown facility on June 11, 2014 and February 11, 2015. FDA acknowledges receipt of your facility's responses to these Form FDA 483s, dated July 2, 2014, September 10, 2014, December 5, 2014, March 4, 2015, May 11, 2015 and May 14, 2015, and October 26, 2015.

FDA issued a Form FDA 483 to your San Diego facility on August 8, 2014. FDA acknowledges receipt of your responses to this Form FDA 483, dated August 29, 2014, October 24, 2014, December 8, 2014, and October 23, 2015.

Based on these inspections, it appears both facilities are 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 at both the Allentown facility and the San Diego facility 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 investigators observed significant CGMP violations at both facilities, causing your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA.

In addition, the FDA investigators observed that both facilities failed to meet the conditions of section 503B. For example, during the 2014 inspections, FDA investigators noted that some of your drug products at the Allentown facility did not include the statement, "This is a compounded drug" on the labeling, and some of your San Diego facility's drug product containers do not include information to facilitate adverse event reporting: www.fda.gov/medwatch and 1-800-FDA-1088. [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

FDA investigators noted that drug products compounded in your Allentown and San Diego facilities 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 that operators at the Allentown facility working in the ISO-5 units blocked unidirectional airflow coming from the HEPA filter during production. The investigators also observed that operators at the San Diego facility process and release drug products without sterility and endotoxin testing. Therefore, your products may be produced in an environment that poses a significant contamination risk.

FDA investigators also noted CGMP violations at your Allentown and San Diego facilities, causing your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations noted at one or both of these facilities include, for example:

1. Your firm have 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 C.F.R. § 211.192).

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 cleaning and disinfecting the room and equipment to produce aseptic conditions (21 CFR 211.42(c)(10)(v)).

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 monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

6. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of such stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)).

7. Your firm do 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). The introduction or delivery for introduction into interstate commerce of these 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

FDA acknowledges your action on December 17, 2014, to voluntarily recall 187 doses of Total Parenteral Nutrition (TPN) products (lot 37-74816) compounded on December 15, 2014. FDA further acknowledges receipt of your responses to the Form FDA 483s issued at both of your facilities. We have reviewed your responses to the observations and while some appear adequate, others are deficient. For example, it is noted that multiple sterility failures have occurred . Your investigations into these failures and corrective actions are inadequate. Your firm does not routinely identify microbial contaminants in the aseptic processing areas when total numbers of colony-forming units (CFU's) are below action levels. Therefore you have no assurance that your cleaning and disinfecting programs have sufficiently removed the identified sterility-failure contaminant from the environment. In addition, it is noted that your study demonstrating the **(b)(4)** used by your firm, **(b)(4)**, is flawed, as you appear to have used **(b)(4)**. This is evident by considerable microbial reduction of the number of CFU's of **(b)(4)** recovered after exposure to **(b)(4)**.

Regarding the labeling observations in the Form FDA 483s issued to your Allentown and San Diego facilities, the corrective actions identified in your responses supported by the documentation that you submitted appear adequate.

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.

D. Conclusion

The violations cited in this letter are not intended to be an all-inclusive statement of violations at your facilities. 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 (15) 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-PHI-11). Please address your reply to Richard Cherry, Compliance Officer, U.S. Food and Drug Administration, 900 U.S. Customhouse, 200 Chestnut Street, Philadelphia, Pennsylvania 19106.

If you have questions regarding the contents of this letter, please contact Mr. Cherry at (215) 717-3075.

Sincerely,
/S/
Annie E. Johnson
District Director
Philadelphia District

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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.