Banner Pharmacy Services, LLC 5/5/16

Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Los Angeles District
Pacific Region
19701 Fairchild
Irvine, CA 92612-2506

Telephone: 949-608-2900
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WARNING LETTER

VIA UNITED PARCEL SERVICE
SIGNATURE REQUIRED

May 5, 2016

WL # 30-16

Pam Nenaber, CEO
Banner Pharmacy Services, LLC
1441 N. 12th Street
Phoenix, AZ 85006

Dear Ms. Nenaber:

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 December 26, 2013, January 27, 2015, and December 28, 2015. From March 16, 2015, to March 20, 2015, FDA investigators inspected your facility, Banner Pharmacy Services, LLC, located at 7300 W Detroit St, Chandler, AZ 85226-2410. During the inspection, the investigators observed serious deficiencies in your practices for producing sterile drug products, which put patients at risk. For example, the investigators noted that your facility is not adequately designed for sterile drug production. Specifically, your facility was not in a good state of repair as investigators observed the ISO 5 area contained peeling paint and dark yellow residues on the walls. In addition, your ISO 5 area is not separated from the ISO 7 area in a way that allows for adequate pressure differentials to be maintained between areas of different air classifications. Your facility lacks pressure gauges to monitor pressure differentials between the ISO 5 area and the ISO 7 area. In addition, gowning procedures are inadequate and allow for bare hands in the ISO 7

area. Investigators observed operators with exposed foreheads in the ISO 7 area. Moreover, your firm uses non–sterile disinfectant in the ISO 7 and ISO 5 areas and on the equipment. 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 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 March 20, 2015. FDA acknowledges receipt of your facility's response, dated April 24, 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 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, the 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.

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 that some of your facility's drug products do not include the following on the label: the statement, "This is a compounded drug;" your facility's name, address, and phone number; the lot or batch number; the established name of the drug, the dosage form and strength, the statement of quantity or volume, as appropriate; the date that the drug was compounded; the storage and handling instructions; the statement, "Not for resale." The inactive ingredients, identified by established name and the quantity or proportion of each ingredient is not included on the label or the container for some of your facility's drug products. Furthermore, the following information is not found on the containers for some drug products you produce: 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

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 noted that your facility is not adequately designed for sterile drug production. Specifically, your facility was not in a good state of repair as investigators observed the ISO 5 area contained peeling paint and dark yellow residues on the walls. In addition, your ISO 5 area is not separated from the ISO 7 area in a way that allows for adequate pressure differentials to be maintained between areas of different air classifications. Your facility lacks pressure gauges to monitor pressure differentials between the ISO 5 area and the ISO 7 area. In addition, gowning procedures are inadequate and allow for bare hands in the ISO 7 area. Investigators observed operators with exposed foreheads in the ISO 7 area. Moreover, your firm uses non–sterile disinfectant in the ISO 7 and ISO 5 areas and on the equipment. 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.

FDA investigators 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 establish an adequate air supply filtered through high-efficiency particulate air filters under positive pressure in the aseptic processing areas. (21 CFR 211.42(c)(10)(iii))

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 ensure that floors, walls and ceilings in the aseptic processing areas are smooth and hard surfaces that are easily cleanable. (21 CFR 211.42(c)(10)(i))

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

5. Your firm failed to ensure the system for cleaning and disinfecting equipment is adequate to produce aseptic conditions. (21 CFR 211.42(c)(10)(v))

6. 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)

7. Your firm failed to adequately design the facility with adequate separation or defined areas or such other control systems necessary to prevent contamination or mix-ups. (21 CFR 211.42(c))

8. Your firm failed to ensure that manufacturing personnel wear clothing appropriate to protect drug product from contamination. (21 CFR 211.28(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

In your April 24, 2015, response, you described certain corrective actions in response to the Form FDA 483 observations. Your proposed corrective actions are deficient. For example, in your response, while you commit to correct the observed 503B labeling deficiencies by including all information required under section 503B on certain product labels and containers, you assert that "the Total Parenteral Nutrition (TPN) product referenced in Observation 11 [of the Form FDA 483] is a patient-specific traditional compounding Section 503A product rather than a Section 503B product to which the statutory labeling information relates." FDA reminds you that drug products produced in a 503B-registered outsourcing facility must be labeled in accordance with section 503B as one of the conditions necessary to qualify for the exemptions under section 503B of the FDCA (Section 503B(a)(11), [21 U.S.C. § 353b(b)(2)]).[4]

Your firm's corrective actions appear to address the GMP deficiencies; however, your response does not include sufficient documentation for us to fully evaluate the adequacy of such actions. For example, you indicate that pressure differentials will be monitored, and that the plastic curtains provided adequate separation between the ISO 5 and ISO 7 areas, however, you did not provide the revised policies and procedures for us to evaluate these corrections. In addition, the noted repairs and subsequent cleaning of the ISO 5 areas cannot be evaluated due to a lack of supporting documentation. Your response did not indicate a timeframe for implementation of some of your proposed corrective actions nor did it include appropriate interim actions to address deficiencies until corrections are implemented.

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 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 (WL # 30-16). Please address your reply to:

Larry H. Howell CAPT USPHS
Acting Director, Compliance Branch
FDA Los Angeles District Office
U.S. Food and Drug Administration
19701 Fairchild
Irvine, CA 92612

If you have questions regarding the contents of this letter, please contact Raymond Brullo, Compliance Officer, at 949-608-2918 or Raymond.Brullo@fda.hhs.gov.

Sincerely,
/S/
CDR Steven E. Porter, Jr.
Los Angeles District Director

Cc:
Virginia Herold, Executive Officer
California State Board of Pharmacy
1625 N. Market Boulevard, Suite N-219

Sacramento, CA 95834

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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.

[4] One of the conditions that must be met in order for a drug product to qualify for the exemptions provided in section 503B is that "[T]he drug is compounded in an outsourcing facility in which the compounding of drugs occurs only in accordance with [section 503B]." [Section 503B(a)(11) of the FDCA [21 U.S.C. §353b(a)(11)]].