Premier Pharmacy Labs Inc 4/27/15

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Florida District
555 Winderley Place, Suite 200
Maitland, Florida 32751

Telephone: 407-475-4700
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VIA UPS NEXT DAY AIR
w/ DELIVERY CONFIRMATION

WARNING LETTER
FLA-15-22
April 27, 2015

Vern A. Allen
Owner/Pharmacist
Premier Pharmacy Labs, Inc. (dba Rx Nations)
8265 Commercial Way
Weeki Wachee, FL 34613-4511

Dear Mr. Allen:

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 April 16, 2014, and again on December 18, 2014. From April 10, 2014 to May 9, 2014, an FDA investigator inspected your facility, Premier Pharmacy Labs, Inc., dba Rx Nations, located at 8265 Commercial Way, Weeki Wachee, FL 34613-4511. [2] During the inspection, the FDA investigator observed serious deficiencies in your practices for producing sterile drug products, which put patients at risk. For example, your firm did not monitor throughout the day the air pressure differentials from the ISO 7 areas and the ante room to the surrounding non-classified area and only infrequently performed personnel monitoring of operators involved in the production of sterile drug products. Your firm also failed to demonstrate through appropriate studies that your hoods are able to provide adequate protection of the ISO 5 areas in which sterile products are produced. 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

firm on May 9, 2014. FDA acknowledges receipt of your facility's response to the Form FDA 483, dated May 29, 2014.

Based on FDA's 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 FDA 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. You also produced a drug product recognized in an official compendium, the United States Pharmacopeia (USP), and the quality and purity 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 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 product labels do not include the statement, "This is a compounded drug." In addition, some of your drug product containers do not include information to facilitate adverse event reporting, and some of your drug products 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. (Section 503B(a)(10) of the FDCA [21 U.S.C. § 353b(a)(10)]).

Furthermore, your facility failed to submit a complete report to FDA upon initial registration as an outsourcing facility in April 2014 identifying all of the drug products that you compounded during the previous 6-month period. FDA notes that the reports your facility submitted in June and December 2014, which only include sterile drugs, may also be incomplete in identifying all of the drug products compounded by your facility if you compounded non-sterile drugs from December 2013 through November 2014. Section 503B(b)(2) of the FDCA [21 U.S.C.

§ 353b(b)(2)] concerning the product reporting requirement for outsourcing facilities is not limited to sterile drugs.

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.[3]

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 that your firm does not monitor throughout the day air pressure differentials from the ISO 7 areas and the ante room to the surrounding non-classified area and only infrequently performs personnel monitoring, including fingertip sampling, of operators involved in the production of sterile drug products. The investigator also observed that your firm failed to demonstrate through appropriate studies that your hoods are able to provide adequate protection of the ISO 5 areas in which sterile products are produced. Therefore, your products may be produced in an environment that poses a significant contamination risk.

Furthermore, FDA analysis of an injectable drug product you produced revealed that it was adulterated under section 501(b) of the FDCA. On July 19, 2013, before you registered your facility as an outsourcing facility, you received a complaint from **(b)(4)** describing an incident on July 19, 2013 where a pharmacy technician withdrew solution from two vials of your Multi Trace 4 Concentrate P.F. INJ drug product into syringes, and noticed flaky green-brown particles or stringy filament in the syringes. Although you closed the complaint investigation after concluding the hospital was culpable, FDA analysis of several intact vials collected on July 31, 2013 of the same product produced by your firm identified particulates that were consistent with material of the crimp cap. 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 quality and purity of your Multi Trace 4 drug product fell below the standards set for the drug in the official USP monograph for Trace Elements Injection, causing it to be adulterated under section 501(b) of the FDCA.

The 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 establish an adequate system for maintaining equipment used to control the aseptic conditions (21 CFR 211.42(c)(10)(vi).

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

3. Your firm failed to thoroughly investigate 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).

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 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(b)).

6. Your firm failed to establish written standards or specifications, methods of testing, methods of cleaning, and methods of sterilization to remove pyrogenic properties (21 CFR 211.94(d)).

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.**[4]** 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). The introduction or delivery for introduction into interstate commerce of these products therefore violates section 301(a) of the FDCA. 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 complete report to FDA upon initial registration as an outsourcing facility in April 2014 identifying all of the drug products that you compounded during the previous 6-month period. (Section 503B(b)(2) of the FDCA). 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 May 29, 2014 response, 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, you did not provide evidence that smoke studies were conducted under dynamic conditions (e.g., videos, reports) or evidence that pressure differentials were monitored during production (e.g., results of such monitoring). In addition, your SOP 220.2 "Environmental Monitoring of Sterile Compounding Areas" does not include a map of air sampling sites; permits an action limit of up to 3 CFU's in ISO 5 areas without scientific justification; and does not address fingertip sampling of operators participating in the production of sterile drugs. Furthermore, you did not provide a rationale for environmental monitoring surface sampling site selection (i.e., the absence of samples in the middle of the clean rooms).

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, 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 contract testing laboratories to perform some of the required testing of your finished drug products. FDA inspected these laboratories in 2012 and 2013 and observed deficiencies in their practices. 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 (FLA-15-22). Please address your reply to Carla Norris, Compliance Officer, at the address above. If you have questions regarding the contents of this letter, please contact Carla Norris at 407-475-4730.

Sincerely,
/S/
Susan M. Turcovski
Director, Florida District

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[1] *See* Pub. L. No. 113-54, § 102(a), 127 Stat. 587, 587-588 (2013).

[2] Previously, in July 2013, FDA had received a report describing possible contamination in a drug product that you compounded, and FDA analysis of samples of the drug product that investigators collected from your facility identified particulate matter.

[3] See, e.g., section 503B(a)(11) of the FDCA [21 U.S.C. § 353b(a)(11)].

[4] 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.