RX South DBA RX3 Compounding Pharmacy LLC 10/23/14

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Baltimore District Office
Central Region
6000 Metro Drive, Suite 101
Baltimore, MD 21215

Telephone: (410) 779-5455
FAX: (410) 779-5707

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER

October 23, 2014

Christopher K. Currin, R.Ph., Managing Partner and Director of Pharmacy
RX South, LLC (dba RX3 Compounding Pharmacy)
12230 Iron Bridge Rd., Suite C
Chester, VA 23831-1534

Dear Mr. Currin:

From January 24, 2014 to February 21, 2014, a U.S. Food and Drug Administration (FDA) investigator conducted an inspection of your facility, RX South (dba RX3 Compounding Pharmacy), located at 12230 Iron Bridge Rd., Suite C, Chester VA 23831-1534. This inspection was conducted after receipt of a complaint about particulate matter in an injection of hydroxyprogesterone caproate solution prepared by your firm.

During the 2014 inspection, the investigator noted that you were not receiving valid prescriptions for individually-identified patients for a portion of the drug products you were producing. In addition, the investigator observed serious deficiencies in your practices for producing sterile drug products, which put patients at risk. For example, our investigator observed that operators did not routinely wipe down materials, such as syringes and filters, with sterile disinfectant before transferring these materials from the unclassified areas into the cleanroom and into the ISO 5 areas. In addition, our investigator found 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 processed. Therefore, your products may be produced in an environment that poses a significant contamination risk.

A Form FDA-483 was issued to your firm on February 21, 2014. Based on this inspection, it appears that you are producing drugs that violate the Federal Food, Drug, and Cosmetic Act (FDCA).

Your firm has a history of poor sterile practices. The Agency previously inspected your firm on December 4-7, 12, and 14, 2012. During the 2012 inspection, FDA observed poor sterile practices at your firm, including inadequate aseptic practices, failure to verify the effectiveness of sterilization methods uses, and inadequate methods for sterility testing. In addition, the investigator noted that you were not receiving valid prescriptions for individually-identified patients for a portion of the drug products you were producing. FDA issued a Form FDA-483 on December 14, 2012. In your February 4, 2013 response to the Form FDA-483, you committed to correct the violations. On August 13, 2013, FDA sent a letter to the Virginia Board of Pharmacy ("Board") referring for appropriate follow-up FDA's concerns about poor sterile practices observed at your firm, and the Virginia BOP took some actions (see letter dated August 13, 2013, **http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM367633.pdf**). However, as a result of a new complaint about particulate matter in an injection prepared by you, FDA conducted another inspection and determined that poor sterile practices continue to exist at your firm, and you still are not obtaining prescriptions for a portion of the drug products produced by your firm.

A. Compounded Drugs Under the FDCA

Section 503A of the FDCA [21 U.S.C. § 353a] describes the conditions under which certain compounded human drug products are entitled to exemptions from three sections of the FDCA: compliance with current good manufacturing practice (CGMP) (section 501(a)(2)(B)); labeling with adequate directions for use (section 502(f)(1)); and FDA approval prior to marketing (section 505). Receipt of valid prescriptions for individually-identified patients is one of the conditions for the exemptions under section 503A. During the FDA inspection, the investigator observed that your firm does not receive valid prescriptions for individually-identified patients for a portion of the drug products you produce.

Accordingly, the drugs you compound without valid prescriptions for individually identified patients are not entitled to the exemptions in section 503A.**[1]**

B. Violations of the FDCA

The drug products that you manufacture and distribute without valid prescriptions for individually-identified patients are misbranded drugs in violation of section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)].

In addition, your sterile drug products are prepared, packed, or held under insanitary conditions whereby they may have been contaminated with filth, or whereby they may have been rendered injurious to health. As such, all sterile products you manufacture are adulterated within the meaning of section 501(a)(2)(A) [21 U.S.C. § 351(a)(2)(A)] of the FDCA. Furthermore, because you manufacture and distribute a portion of your drugs without valid prescriptions for individually-identified patients, the manufacture of such drugs is also subject to FDA's Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations (CFR), Parts 210 and 211. An FDA investigator observed significant CGMP violations at your facility, causing such drug product(s) to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA [21 U.S.C. § 351(a)(2)(B)].

Misbranded Drug Products

Because the drug products for which you have not obtained valid prescriptions for individually-identified patients are intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners, 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].

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 of the components used to make the drug and results in the drug being misbranded.

Adulteration Charges

Additionally, an FDA investigator observed that your sterile drug products 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 operators did not routinely wipe down materials, such as syringes and filters, with sterile disinfectant before transferring these materials from the unclassified areas into the cleanroom and into the ISO 5 areas. In addition, the investigator found 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 processed. Therefore, your products may be produced in an environment that poses a significant contamination risk.

The FDA investigator also observed CGMP violations at your facility, causing the drug products for which you have not obtained valid prescriptions for individually-identified patients to be adulterated under 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 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)).

3. 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)).

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

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 of the components used to make the drug and results in the drug being adulterated.

C. Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product

Section 503A of the FDCA also addresses the compounding of commercially available drug products. For a drug to satisfy the conditions in section 503A, a pharmacist or physician may "not compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product" [21 U.S.C. § 353a(b)(1)(D)].

Section 503A also provides that a drug product is not essentially a copy of a commercially available drug product if it includes a change from the commercially available product that was made for an identified individual patient, and a prescribing practitioner determined that the change produces a significant difference for that patient between the compounded drug product and the commercially available drug product [21 U.S.C. § 353a(b)(2)].

During the most recent inspection of your facility in January-February 2014, the FDA investigator observed that your firm compounded 17-hydroxyprogesterone caproate (17-P). 17-P is the active ingredient in Makena, which FDA approved in February 2011 for the reduction of the risk of certain preterm births in women who have had at least one prior preterm birth. Based on records obtained during the inspection, it appears you are compounding 17-P with a **(b)(4)** base, rather than the castor oil base used in Makena. FDA is not aware of any scientifically reliable evidence demonstrating that compounding 17-P in an **(b)(4)** base different than the oil base used in Makena produces a significant difference for an identifiable group of patients (aside from the rare patient who is known to be allergic to the oil base), and FDA is also not aware of any evidence indicating that the 17-P compounded by your firm produced a significant difference for the patients who received the compounded 17-P as compared to the approved product. Therefore, your compounded 17-P appears to be essentially a copy of the commercially available drug product Makena, and may not be entitled to the exemptions for certain compounded drugs in section 503A of the FDCA.

D. Corrective Actions

We acknowledge your action on January 30, 2014, to voluntarily recall lot 12052013:03 of 17-P (in oil), and your letter dated January 31, 2014, in which you state your firm's decision to discontinue sterile production of 17-P (in oil) injection 250 mg/mL solution as of that day.

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.

In your response to the Form FDA 483 dated March 5, 2014, you referenced your purported compliance with the United States Pharmacopeia (USP)-National Formulary (NF) General Chapter <797> Pharmaceutical Compounding--Sterile Preparations. As noted above your firm has manufactured and distributed drugs without valid prescriptions for individually-identified patients, and the manufacture of such drugs is subject to FDA's drug CGMP regulations, 21 CFR parts 210 and 211.

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 a contract testing laboratory to perform some of the required testing of your finished drug products. FDA inspected this laboratory in 2012 and observed deficiencies in its 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 your compounded drug products are neither adulterated nor misbranded. *See* 21 CFR 210.1(b), 21 CFR 200.10(b).

In addition, you should also correct the violations of sections 501(a)(2)(A) and 502(f)(1) of the FDCA, noted above.

E. 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 and 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.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that 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. Your written notification should be addressed to:

Ernest F. Bizjak, Compliance Officer
FDA Baltimore District Office
U.S. Food and Drug Administration
6000 Metro Drive, Suite 101
Baltimore, MD 21215

If you have questions regarding any issues in this letter, please contact Mr. Bizjak via email at **ernest.bizjak@fda.hhs.gov** or by phone at 410-779-5715.

Sincerely,
/S/
Evelyn Bonnin
District Director
Baltimore District

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[1]The CQA contains a number of other provisions, including new exemptions and requirements for compounders seeking to operate as outsourcing facilities. A discussion of the CQA and the agency's plans to implement the new law may be found at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm

Company Response Letter

- **RX South DBA RX3 Compounding Pharmacy LLC - Response Letter 11/12/14**