Guardian Pharmacy Services 11/3/17

U.S. FOOD & DRUG ADMINISTRATION

Office of Pharmaceutical Quality Operations, Division II
4040 N. Central Expressway, Suite 300
Dallas, Texas 75204

November 3, 2017

CMS Case # 534027

WARNING LETTER

VIA UPS EXPRESS

Jack R. Munn, Owner
JMA Partners, Inc., dba Guardian Pharmacy Services
7920 Elmbrook Drive, Suite 108
Dallas, Texas 75247-4933

Dear Mr. Munn:

From September 12, 2016, to October 21, 2016, U.S. Food and Drug Administration (FDA) investigators inspected your facility, JMA Partners, Inc. dba Guardian Pharmacy Services, located at 7920 Elmbrook Drive, Suite 108, Dallas, Texas 75247-4933. During the inspection, the investigators noted that drug products you produced failed to meet the conditions of section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA) [21 U.S.C. § 353a] for exemption from certain provisions of the FDCA. In addition, the investigators noted serious deficiencies in your practices for producing sterile drug products, which put patients at risk.

We also note that FDA received adverse event reports on April 5, 2017, and June 1, 2017, and conducted follow-up discussions concerning at least 43 patients who experienced vision impairment and loss after being administered intravitreal injections of a drug containing triamcinolone and moxifloxacin compounded by your firm. FDA continues to investigate these adverse events.

FDA issued a Form FDA 483 to your firm on October 21, 2016. FDA acknowledges receipt of your facility's response, dated November 7, 2016. FDA also acknowledges your voluntary recall of 180 syringes of injectable Lidocaine HCl/Sodium Bicarbonate PF (Lot # 50699:00; expiration October 4, 2016), initiated on September 23, 2016, as

a result of a sterility failure. Based on this inspection, it appears that you produced drug products that violate the FDCA.

A. Compounded Drug Products Under the FDCA

Section 503A of the FDCA describes the conditions under which human drug products compounded by a licensed pharmacist in a State licensed pharmacy or a Federal facility, or a licensed physician, qualify for exemptions from three sections of the FDCA: compliance with current good manufacturing practices (CGMP) (section 501(a)(2)(B)); labeling with adequate directions for use (section 502(f)(1)); and FDA approval prior to marketing (section 505) [21 U.S.C. §§ 351(a)(2)(B), 352(f)(1) and 355(a)].[1] Receipt of valid prescriptions for individually-identified patients is one of the conditions for the exemptions under section 503A.

In addition, for a compounded drug product to qualify for the exemptions under section 503A, bulk drug substances used to compound it must: (I) comply with the standards of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, if a monograph exists, and the USP chapter on pharmacy compounding; (II) if such a monograph does not exist, be components of drugs approved by the Secretary; or (III) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, appear on a list developed by the Secretary through regulation ("503A bulks list") (section 503A(b)(1)(A)(i) of the FDCA).

B. Failure to Meet the Conditions of Section 503A

During the inspection, the FDA investigators noted that drug products produced by your firm failed to meet the conditions of section 503A. Specifically, the investigators collected evidence that indicates:

1. Your firm did not receive valid prescriptions for individually-identified patients for a portion of the drug products you produced.

2. Your firm compounded drug products using grape seed oil. Drug products compounded using grape seed oil are not eligible for the exemptions provided by section 503A(a), because these bulk drug substances are not the subject of applicable USP or NF monographs, are not components of FDA-approved human drugs, and do not appear on the 503A bulks list.[2]

Therefore, you compounded drug products that do not meet the conditions of section 503A and are not eligible for the exemptions from the FDA approval requirement of section 505 of the FDCA, the requirement under section 502(f)(1) of the FDCA that labeling bear adequate directions for use, and the requirement of compliance with CGMP under section 501(a)(2)(B) of the FDCA. In the remainder of this letter, we refer to your drug products that do not qualify for exemptions under section 503A as the "ineligible drug products."

Specific violations are described below.

C. Violations of the FDCA

Adulterated Drug Products

The FDA investigators noted that drug products 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 [21 U.S.C. § 351(a)(2)(A)]. For example, the investigators observed that your firm used non-sterile wipes and a non-sterile disinfectant as part of your disinfection program for the aseptic processing areas. Our investigators also observed that one of the laminar flow hoods in your cleanroom consisted of a **(b)(4)** table supported by a particle board.

Furthermore, the manufacture of the ineligible drug products is subject to FDA's CGMP regulations, Title 21, Code of Federal Regulations (CFR), parts 210 and 211. The FDA investigators observed significant CGMP violations at your facility, causing the ineligible drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations included, for example:

1. 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)).

2. Your firm failed to maintain the buildings used in the manufacture, processing, packing, or holding of a drug product in a clean and sanitary condition (21 CFR 211.56(a)).

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 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)).

5. 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 [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.

Misbranded Drug Products

The ineligible drug products you compounded are intended for conditions 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.[3] Accordingly, these ineligible drug products are misbranded under section 502(f)(1) 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.

D. Corrective Actions

We have reviewed your firm's response to the Form FDA 483. FDA acknowledges your voluntary recall of 180 syringes of injectable Lidocaine HCl/Sodium Bicarbonate PF (Lot # 50699:00; expiration October 4, 2016), initiated on September 23, 2016, as a result of a sterility failure.

Regarding the insanitary conditions observed during the inspection, your corrective actions appear deficient in that:

1. You did not commit to cease the use of non-sterile wipes in the disinfection of the aseptic processing areas. The use of non-sterile wipes increases the potential for contamination to be introduced into the aseptic processing areas.

2. You did not commit to cease the use of a non-sterile disinfectant in the aseptic processing areas. It appears from your revised SOP 3.020, Cleaning and Maintenance of the Cleanroom Facility, that your firm will continue to use a non-sterile disinfectant, **(b)(4)**, to disinfect the ISO 5 classified areas. A non-sterile disinfectant may introduce spore contamination into ISO 5 areas and wiping with **(b)(4)** afterwards would not eliminate spores. Moreover, your revised SOP did not include disinfectant contact times. You should ensure the disinfectant contact time, particularly for your sporicidal agent, is sufficient to achieve adequate levels of disinfection.

3. Regarding the laminar flow hood supported by the particle board within your cleanroom, you stated in your response dated November 7, 2016, that "Within **(b)(4)** months the **(b)(4)** Laminar Flow Hood shall be modified to ensure compliance." However, you did not describe an actual plan for modification or provide any supporting documentation. Therefore, it is unclear if the particle board is still in your cleanroom while aseptic production occurs. Particle board is particle-generating, difficult to clean, and can harbor contamination.

Please be aware that section 501(a)(2)(A) of the FDCA concerning insanitary conditions applies regardless of whether drug products you compound meet the conditions of section 503A, including the condition on receipt of a prescription for an identified individual patient prior to compounding and distributing drug products and the condition on compounding drug products using a bulk drug substance that complies with an applicable USP or NF monograph, is a component of an FDA-approved human drug, or appears on the 503A bulks list.

In your response to the Form FDA 483 you state, "As a Section 503A pharmacy compliant with Texas State law . . . GPS is not required to meet the CGMP regulations that are cited within the Form 483." You specifically reference FDA's Final Guidance, Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act published in the Federal Register on July 2, 2014 (79 FR 37742), as well as "the most recently released FDA inspections notice stating that FDA will not cite violations based on cGMP regulations for 503A pharmacies."

As stated in FDA's July 11, 2016 notice, "[i]f the investigator issues a 'Form FDA-483' list of inspectional observations to the firm, the investigator will *not* include observations that represent deviations solely from FDA's current good manufacturing practice (CGMP) requirements unless it appears, based on the investigator's preliminary assessment, that the firm compounds drugs that do not qualify for the exemptions under section 503A."

As explained above, receipt of valid prescriptions for individually-identified patients and the compounding of drug products using a bulk drug substance that complies with an applicable USP or NF monograph, is a component of an FDA-approved human drug, or appears on the 503A bulks list are conditions of section 503A, which your firm failed to meet for a portion of the drug products you produced. Therefore, the inclusion of observations that represent deviations from CGMP requirements on the Form FDA-483 was appropriate.

Should you continue to compound and distribute drug products that do not meet the conditions of section 503A, the compounding and distribution of such drugs would be subject to the new drug approval requirement, the requirement to label drug products with adequate directions for use, and the drug CGMP regulations. Before doing so, you must comply with the requirements of section 505 and 502(f)(1) and fully implement corrections that meet the minimum requirements of the CGMP regulations.[4]

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. 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 produce are neither adulterated nor misbranded. [*See* 21 CFR 210.1(b), 21 CFR 200.10(b)].

FDA strongly recommends that your management undertake a comprehensive assessment of operations, including facility design, procedures, personnel, processes, maintenance, materials, and systems. In particular, this review should assess your aseptic processing operations. A third party consultant with relevant sterile drug manufacturing expertise should assist you in conducting this comprehensive evaluation.

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, 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.

Within fifteen (15) working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct the violations. Please include an explanation of each step being taken to prevent the recurrence of the 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 you cannot complete corrective action within fifteen (15) working days, state the reason for the delay and the time within which you will complete the correction.

Your written notification should refer to the Warning Letter Number above (**CMS Case # 534027**).

Please address your reply to John W. Diehl, Acting Director, Compliance Branch, at the FDA address provided. In addition, please submit a signed copy of your response to john.diehl@fda.hhs.gov.

If you have questions regarding the contents of this letter, you may contact Mr. Diehl at (214) 253-5288.

Sincerely,
/S/
Monica R. Maxwell
Acting Program Division Director
Office of Pharmaceutical Quality Operations, Division II

CC:

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[1] We remind you that there are conditions other than those discussed in this letter that must be satisfied to qualify for the exemptions in section 503A of the FDCA.

[2] On June 9, 2016, FDA issued a final guidance titled, *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act*. This guidance describes FDA's interim regulatory policy for State-licensed pharmacies, Federal facilities, and licensed physicians that compound human drug products using bulk drug substances that do not otherwise meet the conditions of section 503A(b)(1)(A)(i) while the 503A bulks list is being developed. Specifically, the guidance sets out the conditions under which FDA does not intend to take action against a State-licensed pharmacy, Federal facility, or licensed physician for compounding a drug product using a bulk drug substance that is not the subject of an applicable USP or NF monograph or a component of an FDA-approved drug, until the substance is identified in a final rule as included or not included on the 503A bulks list. These conditions include that the substance may be eligible for inclusion on the 503A bulks list, was nominated with adequate support for FDA to evaluate it, and has not been identified by FDA as a substance that appears to present significant safety risks pending further evaluation. Grape seed oil was nominated for inclusion on the 503A bulks list; however, it was not nominated with adequate support for FDA to evaluate the substances. For additional information, see the guidance at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469120.pdf.

[3] Your ineligible drug products are not exempted from the requirements of section 502(f)(1) of the FDCA by regulations issued by the FDA (see, e.g., 21 CFR 201.115).

[4] In this letter we do not address whether your proposed corrective actions would resolve the CGMP violations noted above.