WARNING LETTER

Imprimis NJOF, LLC

MARCS-CMS 553322 — JUN 07, 2019

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Pramod K. Sharma

Vice President, Quality

Imprimis NJOF, LLC

1705 Route 46 Suite 6B
Ledgewood, NJ 07852-9720
United States

Issuing Office:

Division of Pharmaceutical Quality Operations I

10 Waterview Blvd, 3rd Floor
Parsippany, NJ 07054
United States

WARNING LETTER
CMS # 553322

June 7, 2019

VIA UPS OVERNIGHT

Pramod K. Sharma, Vice President, Quality
Imprimis NJOF, LLC
1705 Route 46 Suite 6B
Ledgewood, NJ 07852-9720

Dear Dr. Sharma:

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 November 12, 2016, and most recently on October 26, 2017. From April 24, 2017, to July 10, 2017, FDA investigators inspected your facility, Imprimis NJOF, LLC, located at 1705 Route 46 Suite 6B, Ledgewood, NJ 07852-9720. During the inspection, the investigators noted that drug products you produced failed to meet the conditions of section 503B of the FDCA necessary for drugs produced by an outsourcing facility to qualify for exemptions 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.

FDA issued a Form FDA 483 to your facility on July 10, 2017. FDA acknowledges receipt of your facility's responses, dated July 21, 2017, October 31, 2017, and December 13, 2017. Based on this inspection, it appears you produced drugs that violate the FDCA.

A. Compounded Drug Products under the FDCA

Under section 503B(b) of the FDCA, 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 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.***2***

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 applicable provisions of the FDCA, including section 501(a)(2)(B) [21 U.S.C. § 351(a)(2)(B)], regarding current good manufacturing practice (CGMP), section 501(a)(2)(A) [21 U.S.C. § 351(a)(2)(A)], regarding insanitary conditions, and section 501(d) [21 U.S.C. § 351(d), regarding quality or strength of a drug. 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.

In addition, for a compounded drug product to qualify for the exemptions under section 503B, bulk drug substances used to compound it must appear on a list established by the Secretary identifying bulk drug substances for which there is a clinical need ("503B bulks list"), or that appear on the drug shortage list in effect under section 506E of the FDCA at the time of compounding, distribution, and dispensing (section 503B(a)(2)(A)(i) of the FDCA [21 U.S.C. § 353b(a)(2)(A)(i)]).

In addition, for a compounded drug product to qualify for the exemptions under section 503B, it must be compounded in an outsourcing facility that is in compliance with the registration and reporting requirements in section 503B(b) including the requirement to submit a report to FDA upon initially registering as an outsourcing facility, once in June of each year, and once in December of each year identifying the drug products compounded during the previous 6-month period (section 503B(b)(2) of the FDCA [21 U.S.C. §353b(b)(2)]).

Further, for a compounded drug product to qualify for the exemptions under section 503B, it must submit adverse event reports in accordance with the content and format requirements established through guidance or regulation under 21 CFR 310.305 (section 503B(b)(5) of the FDCA [21 U.S.C. § 353b(b)(5)]).

B. Failure to Meet the Conditions of Section 503B

During the inspection, FDA investigators noted that drug products produced by your facility failed to meet the conditions of section 503B. For example, the investigators noted:

1. Your facility compounded drug products using gatifloxacin. Drug products compounded using gatifloxacin are not eligible for the exemptions provided by section 503B, because gatifloxacin does not appear on the 503B bulks list and is not used to compound a drug that appears on the drug shortage list.***3***

2. Your firm failed to submit a report to FDA identifying the drug products that you compounded during the previous six months. Specifically, the report to FDA dated June 2017 did not include all the drug products that you compounded during the previous six months; the following products were compounded during the six months prior to June 2017 and not identified on your report dated June 2017: triamcinolone-moxifloxacin 15mg/1ml ophthalmic injection, prednisonegatifloxacin-nepafenac 1/0.5/0.1% ophthalmic drop, prednisolone-gatifloxacin 1/0.5% ophthalmic drop, prednisolone-nepafenac 1/0.1% ophthalmic drop, and moxifloxacin 5mg/1ml ophthalmic injection.

3. Your firm failed to submit adverse event reports to FDA as required by section 503B(b)(5) and 21 CFR 310.305. Specifically, FDA received your adverse event report on September 18, 2017 regarding a patient who was diagnosed postoperatively with bilateral hemorrhagic occlusive retinal vasculitis (HORV) after being administered injections into both eyes of your compounded triamcinolone, moxifloxacin, and vancomycin (TMV) product after cataract surgery. However, your firm became aware of this adverse event on August 11, 2017. An outsourcing facility must submit to FDA reports of all serious, unexpected adverse events associated with their compounded drug products as soon as possible, but no later than 15 calendar days after first receiving information about the adverse event (21 CFR 310.305).

Because your compounded drug products have not met all of the conditions of section 503B, they are not eligible for the exemptions in that section from the FDA approval requirements of 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.

Specific violations are described below.

C. Violations of the FDCA

Adulterated Drug Products

FDA investigators noted CGMP violations at your facility, that caused 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 system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).
2. Your firm failed to establish and follow appropriate procedures for testing the incoming materials at the time they are selected to determine whether they meet the criteria for use (21 CFR 211.84(d)(3)).
3. Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products (21 CFR 211.22(a)).
4. 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).

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 — 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.

Under section 501(d) of the FDCA [21 U.S.C. § 351(d)], a drug is adulterated if the drug and any substance has been (1) mixed or packed therewith so as to reduce its quality or strength or (2) substituted wholly or in part thereafter. FDA analyzed samples of your triamcinolone moxifloxacin injectable product. FDA identified the presence of the antioxidant 2,2'-Methylenebis (4-methyl-6-tertbutylphenol) in the analyzed samples.

Unapproved New Drug Products

You do not have any FDA-approved applications on file for drug products that you compound.***4*** Under sections 505(a) and 301(d) and of the FDCA [21 U.S.C. §§ 331(d)] a new drug may not be introduced into 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. Marketing of these products, or other applicable products, without an approved application violates these provisions of the FDCA.

Misbranded Drug Products

You compound drug products that 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 causing them to be misbranded under section 502(f)(1) of the FDCA.***5*** The introduction or delivery for introduction into interstate commerce of these products therefore violates section 301(a) of the FDCA. Further, it is also 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's June 2017 report does not identify all 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)].

Failure to Report Adverse Events

As noted above, your facility failed to submit adverse event reports in accordance with section 503B(b) and 21 CFR 310.305. The failure to report adverse events 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)].

D. Corrective Actions

We have reviewed your facility's responses to the Form FDA 483 dated July 21, 2017, October 31, 2017, and December 13, 2017.

Some of your corrective actions appear adequate. However, the following corrective actions appear deficient:

1. You have not adequately addressed the lack of non-viable and viable environmental monitoring during the time the **(b)(4)** and the **(b)(4)** were found to be non-operational. Although your response indicated that there was some control over the microbial environment during the time the continuous non-viable air monitoring was non-operational, surface monitoring, viable monitoring, personnel, media fill studies, and sterility testing are not by themselves adequate substitutes for the non-viable air monitoring.

2. You indicated that you have extended your environmental monitoring program to require **(b)(4)** monitoring following each batch production. However, there is no monitoring of the employee's sleeves or forehead.

3. You have provided **(b)(4)** study results for the incoming plastic bottles that are sterilized by **(b)(4)**; however, you did not specify acceptance criteria. It is unclear whether your firm has an internal procedure for determining what is acceptable.

4. You have not provided evidence to indicate that you can properly evaluate the discrepancies, find true root cause of the issues, and perform impact assessment for your investigations.

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).]

Regarding observations related to the conditions of section 503B of the FDCA, we received your nomination from July 21, 2017 to include gatifloxacin on the 503B bulks list. We will review any drug compounding you may do using these bulk drug substances under the policies described in FDA's final guidance Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act (revised in January 2017).

Should you continue to compound and distribute drug products that do not meet the conditions of section 503B, the compounding and distribution of your drugs would be subject to the new drug approval requirement, the requirement to label drug products with adequate directions for use, and the Drug Supply Chain Security Act requirements.

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.

In addition, it has come to the agency's attention that your firm recently relocated its 503A operations to a different suite situated within the same building as your outsourcing facility establishment. We acknowledge that the 503A and 503B facilities are no longer adjacent. However, for your awareness, in May 2018, FDA

published the final guidance titled, Facility Definition Under Section 503B of the Federal Food, Drug, and Cosmetic Act, which provides the Agency's interpretation of the term "facility" as used in the definition of "outsourcing facility" under section 503B(d), and current thinking regarding how to ensure that the compounding of drugs in an outsourcing facility occurs only in accordance with section 503B.

Further, it has come to the agency's attention that your firm used **(b)(4)** (i.e., the certificate of analysis from **(b)(4)** provides that the **(b)(4)** was "**(b)(4)**)) in the triamcinolone-moxifloxacin injectable product. We remind you that it is your firm's responsibility to ensure that all components used to produce finished drug products are appropriate for the intended route of administration.

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 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. If you cannot complete corrective action within 15 working days, state the reason for the delay and the time within which you will complete the correction.

Send your electronic response to orapharm1_responses@fda.hhs.gov (mailto:orapharm1_responses@fda.hhs.gov). Your written notification should refer to the Warning Letter Number above (#553322).

If you have any questions, contact Compliance Officer, Barbara Wilimczyk-Macri at barbara.wilimczyk@fda.hhs.gov (mailto:barbara.wilimczyk@fda.hhs.gov) or 973-331-4951.

Sincerely,
/S/

Diana Amador-Toro
Program Division Director/District Director
Office of Pharmaceutical Quality Operations
Division I/New Jersey District

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

2 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 503B of the FDCA.

3 On June 9, 2016, FDA issued a final guidance titled, Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act (revised in January 2017). This guidance describes FDA's interim regulatory policy for outsourcing facilities registered under section 503B of the FDCA while the 503B bulks list is being developed. Specifically, the guidance sets out conditions under which FDA does not intend to take action against an outsourcing facility for compounding a drug product using a bulk drug substance that is not included on the 503B bulks list and does not appear on the drug shortage list in effect under section 506E at the time of compounding, distribution, and dispensing until the substance is identified in a final Federal Register notice as included or not included on the 503B bulks list. These conditions include that the substance may be eligible for inclusion on the 503B 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. Gatifloxacin is not eligible for the interim regulatory policy. For additional information, see the guidance at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469122.pdf (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469122.pdf)

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.

5 Your compounded 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).

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