Isomeric Pharmacy Solution, LLC 12/12/16

Denver District Office
6th Ave & Kipling St. (P.O. Box 25087)
Denver, CO 80228

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER

Ref. # DEN-17-02-WL

December 12, 2016

Mr. William Richardson, CEO
Isomeric Pharmacy Solutions, LLC
2401 S. Foothill Drive, Suite D
Salt Lake City, UT 84109-1479

Reference: FEI 3011752429

Dear Mr. Richardson:

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 July 14, 2015, and again on December 31, 2015. From August 24, 2015, to August 28, 2015, and again from June 20, 2016, to June 29, 2016, FDA investigators inspected your facility, Isomeric Pharmacy Solutions, LLC, located at 2401 S. Foothill Drive, Salt Lake City, Utah. During the inspections, 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, investigators noted serious deficiencies in your practices for producing sterile drug products, which put patients at risk. For example, during the 2016 inspection, the investigators observed that glassware used for processing testosterone prior to **(b)(4)** sterilization had visibly burnt, brown, carbon-like staining on the interior surface that would come in contact with drug products. In addition, the investigators observed white stains on the metal

grates covering the HEPA filters in two of your ISO 5 hoods. Furthermore, during both the 2015 and 2016 inspections, 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.

FDA issued a Form FDA 483, Inspectional Observations, to your facility on August 28, 2015, and again on June 29, 2016. FDA acknowledges receipt of your facility's responses, dated September 17, 2015, January 26, 2016, May 12, 2016, and July 15, 2016. FDA also acknowledges your actions on February 2, 2016, June 29, 2016, and August 1, 2016, to voluntarily recall triamcinolone diacetate 40 mg/mL injectable suspension (lots 12042015@3 and 12212015@8), methylprednisolone acetate/lidocaine HCl 40/10 mg/mL injectable suspension (lots 04045 and 04046), and betamethasone acetate/betamethasone sodium phosphate injectable suspension (all lots), respectively. On July 26, 2016, you also agreed to cease production of betamethasone acetate/betamethasone sodium phosphate injectable suspension until adequate corrective actions have been implemented. You should notify FDA before resuming production of betamethasone suspension injectable drug products.

Based on these inspections, it appears your facility is producing drugs that violate the FDCA.

A. Compounded Drugs 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), 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.

In addition, for a compounded drug product to qualify for the exemptions under section 503B, the labeling of the drug must include certain information (section 503B(a)(10) of the FDCA [21 U.S.C. §353b(a)(10)]).

Also, 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)]).

B. Failure to Meet the Conditions of Section 503B

During the most recent 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. Some of your facility's drug products did not include the following statement on the label: "Not for resale." Some of your facility's drug products did not include the following information on the container: A list of inactive ingredients, identified by established name and the quantity or proportion of each ingredient.

2. Your facility failed to submit a report to FDA upon initial registration as an outsourcing facility in July 2015 identifying the drug products that you compounded during the previous 6-month period.

Therefore, you compounded drug products (collectively the "ineligible drug products") that do not meet all of the conditions of section 503B and 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.[3]

Specific violations are described below.

C. Violations of the FDCA

Adulterated Drug Products

During both the 2015 and 2016 inspections, FDA investigators noted that drug products 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 your drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, during the 2016 inspection, the investigators observed that glassware used for processing testosterone prior to **(b)(4)** sterilization had visibly burnt, brown, carbon-like staining on the interior surface that would come in contact with drug products. In addition, the investigators observed white stains on the metal grates covering the HEPA filters in two of your ISO 5 hoods. Furthermore, during both the 2015 and 2016 inspections, 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.

FDA investigators also noted CGMP violations at your facility, that caused your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations identified during the June 2016 inspection included, for example:

1. 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)).

2. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).

3. Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or established requirements (21 CFR 211.67(a)).

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 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 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 establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of such stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)).

8. 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 material, labeling, and drug products (21 CFR 211.22(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 the ineligible drug products that you compounded.[4] Under sections 505(a) and 301(d) 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. Marketing of these products, or other applicable products, without an approved application violates these provisions of the FDCA.

Misbranded Drug Products

The ineligible drug products you compounded are intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners, therefore, 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, and they are not exempt from the requirements of section 502(f)(1) of the FDCA (*see, e.g.,* 21 CFR 201.115). Accordingly, these ineligible drug products are misbranded under section 502(f)(1) of the FDCA. The introduction or delivery for introduction into interstate commerce of these products 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.

Failure to Report Drugs

As noted above, your facility failed to submit a report to FDA upon initial registration as an outsourcing facility in July 2015, identifying 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)].

D. Corrective Actions

We have reviewed your Form FDA 483 responses. In your responses, you described certain corrective actions you have taken or plan to take in response to the Form FDA 483 observations. We acknowledge your recall of triamcinolone diacetate 40

mg/mL injectable suspension (lots 12042015@3 and 12212015@8), methylprednisolone acetate/lidocaine HCl 40/10 mg/mL injectable suspension (lots 04045 and 04046), and betamethasone acetate/betamethasone sodium phosphate injectable suspension (all lots).

In addition, we acknowledge that you ceased production of the betamethasone acetate/betamethasone sodium phosphate injectable suspension product until adequate corrective actions have been implemented. You should notify FDA before resuming production of betamethasone suspension injectable drug products.

Some of your proposed corrective actions appear adequate, but your responses did not include sufficient information or supporting documentation for us to fully evaluate the adequacy of such actions. For example in your July 15, 2016 response, your firm referenced but did not provide a copy of a new cleaning SOP for the stained glassware (Observation 6). We also note that we are concerned with your practice of covering depyrogenated glassware with foil as the seal may not be adequate to prevent contamination. Also, you committed to redoing your smoke studies but you have not provided adequate documentation, such as a detailed description of the conditions at the time of the smoke studies or video taken during the study for our review. Furthermore, the validation of your **(b)(4)** sterilization cycles cannot be evaluated due to a lack of supporting documentation.

Some of the proposed corrective actions in your July 15, 2016 response appear to be deficient. In regards to the environmental monitoring excursions noted in Observation 1E, your firm initiated a corrective and preventative action (CAPA 16019) that you indicated provides for investigation of the quality system concerns. However, you did not provide a copy of the CAPA; nor did you indicate potential root cause, potential impact to sterile drug batches, and changes to be implemented to prevent reoccurrence. Furthermore, your response does not adequately address the recurrence of environmental excursions. In response to the white staining on the metal grates covering the HEPA filters in two of your ISO 5 hoods, you committed to finding an alternative wipe that would allow for hard scrubbing without generating particulates. However, you failed to assess how the shredding of the wipes may have impacted products currently on the market that were produced under the described conditions, as well as products you are producing while locating an alternative wipe. In regard to the container closure integrity observation, you stated that the integrity of the container closure had been established for each of your approved containers and although your stability protocols state that product was stored upright, you verified that the normal practice of your **(b)(4)** is to store them horizontally. However, you did not include any documentation to support the integrity of your container closures throughout their expiry period.

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). Based on the observed deficiencies, it does not appear that your quality system

has the proper controls in place to adequately ensure the accuracy of data to support the safety, effectiveness, and quality of the drugs you produce.
In addition, we note that you have chosen to **(b)(4)** to perform some of the required testing of your finished drug products. It is essential that your **(b)(4)** is qualified and that you maintain sufficient oversight of the **(b)(4)** operations to ensure that it is fully CGMP compliant. Regardless of whether you **(b)(4)**, 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)].

Regarding observations related to the conditions of section 503B of the FDCA, we are unable to fully evaluate your corrective actions due to lack of adequate supporting documentation. You state that you now include all required information on your labels, but you did not provide copies of such labels.

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 first 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 as well as improvements to your quality system. A third party consultant with relevant sterile drug manufacturing expertise should be used to conduct 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 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 you cannot complete the corrective actions within fifteen working days, state the reason for the delay and the time frame within which you will complete the corrections.

Your written notification should refer to the Warning Letter Number above (REF# DEN-17-02-WL). Please address your reply to:

Matthew R. Dionne, Pharm.D.
GDUFA Compliance Officer
U.S. Food and Drug Administration
Denver Federal Center, Bldg. 20
6th Ave and Kipling St. (P.O. Box 25087)
Denver, CO 80225-0087

If you have questions regarding the contents of this letter, please contact Dr. Dionne via email at Matthew.Dionne@fda.hhs.gov or by phone at (303) 236-3064.

Sincerely,
/S/
LaTonya M. Mitchell
District Director
Denver 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] 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.