Gipsco Investment Corp 7/10/18

Division of Pharmaceutical Quality
Operations III
300 River Place, Suite 5900
Detroit, MI 48207
Telephone: (313) 393-8100
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July 10, 2018

WARNING LETTER

Case# 557802

UPS NEXT DAY
SIGNATURE REQUIRED

Beverly E. Israel
Owner
Gipsco Investment Corp.
dba Lee Silsby Compounding Pharmacy
3216 Silsby Road
Cleveland Heights, OH 44118-3428

Dear Ms. Israel:

From June 5, 2017, to June 9, 2017, U.S. Food and Drug Administration (FDA) investigators inspected your facility, Gipsco Investment Corp., dba Lee Silsby Compounding Pharmacy, located at 3216 Silsby Road, Cleveland Heights, OH 44118-3428. 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. Additionally, 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 firm on June 9, 2017. FDA acknowledges receipt of your facility's response, dated June 30, 2017. 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 noted that your firm compounded drug products using melatonin. Drug products compounded using melatonin are not eligible for the exemptions provided by section 503A(a), because melatonin is not the subject of an applicable USP or NF monograph, is not a component of an FDA-approved human drug, and does 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 in that section 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. For example:

1. Investigators observed an operator sitting with her upper body leaning into the ISO-5 classified area with the sleeves of her non-sterile gown resting directly on the work surface of the ISO-5 classified area, thereby providing a potential source of contamination

2. Your firm was found to be using non-pharmaceutical grade **(b)(4)** for blanketing filled vials of sterile glutathione solution for inhalation. The source of the **(b)(4)** is a commercially available **(b)(4)** preservative that is passed through a **(b)(4)** filter.
3. Investigators observed a loose, unsealed light fixture in the ceiling of the **(b)(4)** clean room where **(b)(4)** work stations are housed and where aseptic operations occur. The resulting gap in the ceiling is a contamination risk as it provides an opportunity for particles to enter this classified area.
4. Temperature and time conditions used for heat sterilization are not lethal to heat resistant microorganisms. Investigators noted that your autoclave cycle temperatures are required to reach **(b)(4)**°C. However, autoclave logs for the period from August 10, 2016 through March 28, 2017 indicate the temperature did not exceed **(b)(4)**°C for **(b)(4)** of **(b)(4)** equipment sterilization cycles.

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

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 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.

D. Corrective Actions

We have reviewed your firm's response to the FORM FDA-483. We cannot fully evaluate the adequacy of the following corrective actions described in your response because you did not include sufficient information or supporting documentation:

1. In your response, you commit to using sterile gowns. The response also notes the implementation of a **(b)(4)**, designed to prevent operators' upper body and head from entering the ISO-5 classified area. However, your firm did not provide supporting documentation for our review.
2. In your response, you commit to ceasing the use of **(b)(4)** for blanketing glutathione sterile drug preparations, and that you have amended the master formula for Glutathione Preservative Free Solution (New) 100mg.ml Inhalation. However, your firm did not provide supporting documentation for our review.
3. Your response notes that you repaired a loose, unsealed light fixture in your **(b)(4)** classified room which houses your **(b)(4)** classified workstation, and where sterile drug are produced. However, you did not provide photos or other documentation to support your corrective action.

Moreover, the following corrective action appears inadequate to address the insanitary conditions noted:

In your response, you state your operator(s) erroneously documented incorrect autoclave temperature, and that the instrument will not operate until the appropriate cycle temperature is achieved. However, you failed to provide any documentation to substantiate the assertion that the required cycle parameters, including temperature, time and pressure, were maintained for the equipment sterilization cycles referenced.

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 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.

Regarding issues related to the conditions of Section 503A, you have not addressed the compounding of drug products using melatonin. As explained above, drug products compounded using melatonin are not eligible for the exemptions provided by section 503A(a), because melatonin is not the subject of an applicable USP or NF monograph, is not a component of an FDA-approved human drug, and does not appear on the 503A bulks list.

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 first undertake a comprehensive assessment of operations, including facility design, procedures, personnel, processes, maintenance, materials, and systems. 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 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 fifteen (15) working days, state the reason for the delay and the time within which you will complete the correction.

Please send your electronic reply to: ORAPHARM3_RESPONSES@fda.hhs.gov.

Attn: Russell K. Riley
Compliance Officer
U. S. Food and Drug Administration
Division of Pharmaceutical Quality Operations III

Refer to the Unique Identification Number (Case# 557802) when replying. If you have questions regarding the contents of this letter, please contact Mr. Riley by phone at (630) 323-2763 ext. 101.

Sincerely,
/S/
Art O. Czabaniuk
Program Division Director
Division of Pharmaceutical Quality Operations III

cc:
Adam J. Israel, Manager
Gipsco Investment Corp.
dba Lee Silsby Compounding Pharmacy
3216 Silsby Road
Cleveland Heights, OH 44118-3428

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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. Melatonin was nominated for inclusion on the 503A bulks list. However, it was not nominated with adequate support for FDA to evaluate the substance. 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.