Stonegate Pharmacy LP 11/10/16

U.S. FOOD & DRUG ADMINISTRATION

Dallas District Office
4040 North Central Expressway,
Suite 300
Dallas, TX 75204-3158

November 10, 2016
2017-DAL-WL-03

WARNING LETTER

UPS Overnight
Rene F. Garza, Pharm.D., Chief Executive Officer
Stonegate Pharmacy, LP
2501 W. William Cannon Drive, Suite 203
Austin, Texas 78745-5255

Dear Dr. Garza:

Between February 23, 2016, and March 2, 2016, U.S. Food and Drug Administration (FDA) investigators conducted an inspection of your facility, Stonegate Pharmacy, LP, located at 2501 W. William Cannon Drive, Suite 203, Austin, Texas 78745.

During the inspection, the investigators noted that you did not receive valid prescriptions for individually-identified patients for a portion of the drug products you produced. The investigators also noted that your firm produces domperidone products. Domperidone is not the subject of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, nor is it a component of an FDA-approved human drug product, and it does not appear on a list developed by the Secretary of the Department of Health and Human Services (the Secretary) under section 503A(b)(1)(A)(i)(III) of the Federal Food, Drug, and Cosmetic Act (FDCA) [21 U.S.C. § 353a(b)(1)(A)(i)(III)]. In addition, the investigators observed serious deficiencies in your practices for producing sterile drug products, which put patients at risk. For example, our investigators noted your firm uses non-sterile wipes and non-sterile disinfectants in the ISO 5 area in which sterile products are processed.

FDA issued a FDA 483, Inspectional Observations, to your firm on March 2, 2016. FDA acknowledges your March 30, 2016, response to the FDA 483.

Based on this inspection, it appears that you have produced drugs that violate the Federal Food, Drug, and Cosmetic Act (FDCA).

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 qualify for exemptions from three sections of the FDCA: compliance with current good manufacturing practice (CGMP) requirements, section 501(a)(2)(B) of the FDCA [21 U.S.C. § 351(a)(2)(B)]; labeling with adequate directions for use, section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)]; and FDA approval prior to marketing, section 505 of the FDCA [21 U.S.C. § 355]. Receipt of valid prescriptions for individually-identified patients is one of the conditions for the exemptions under section 503A.

During the FDA inspection, the investigators observed that your firm did not receive valid prescriptions for individually-identified patients for a portion of the drug products you produced.

In addition, compounded drug products containing domperidone are not eligible for the exemptions under section 503A of the FDCA because domperidone 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 a list of bulk drug substances that may be used for compounding developed by the Secretary. [1]

Accordingly, the drugs you compound without valid prescriptions for individually-identified patients, and any drug products you compound using domperidone, are not entitled to the exemptions in section 503A of the FDCA. In addition, we remind you that there are a number of other conditions that must be satisfied to qualify for the exemptions in section 503A of the FDCA.[2]

B. Violations of the FDCA

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

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

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

You compound products containing the bulk drug substance domperidone and drug products for which you have not obtained valid prescriptions for individually-identified patients that are intended for conditions that are 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, 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 and results in the drug being misbranded.

Adulterated Drug Products

Additionally, FDA investigators noted that drug products that are 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, your firm uses non-sterile wipes and non-sterile disinfectants in the ISO 5 area where sterile products are processed.

The FDA investigators also noted 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 ensure the system for cleaning and disinfecting equipment is adequate to produce aseptic conditions. (21 CFR 211.42(c)(10)(v))

2. 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))

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

4. 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))

5. Your firm failed to ensure that manufacturing personnel wear clothing appropriate to protect drug product from contamination. (21 CFR 211.28(a))

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 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))

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 adulterated.

C. Corrective Actions

We have reviewed your firm's planned corrective actions, as documented in your March 30, 2016, response to the FDA 483 that was issued at the close of the inspection. Although some corrective actions described in your response appear to be adequate, others are deficient. Your response does not specifically address the use of non-sterile disinfectants in the ISO 5 laminar flow hood. In addition, your response states that contact time for cleaning agents "if applicable will be noted and adhered to". However, you have not provided information regarding the contact times that will be assigned for each cleaning agent.
Furthermore, your response did not provide adequate scientific justification for the autoclave cycle used to terminally sterilize implantable pellets, including consideration of heat penetration into the container closure and the pellets themselves. You also did not provide information on an investigation that was conducted following the microbial recovery in the ISO 5 area, to include a root cause analysis that assesses the potential impact on products produced under environmental conditions that did not meet acceptable levels of cleanliness.

FDA acknowledges your commitment, as discussed with the investigators during the inspection, to cease the practice of manufacturing and distributing compounded drug products without prescriptions for individually-identified patients.

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.

Please be aware that section 501(a)(2)(A) of the FDCA concerning insanitary conditions applies regardless of whether the drugs are compounded and distributed after receipt of a prescription for an identified individual patient. If you continue to manufacture and distribute drug products without valid prescriptions for individually-identified patients, the manufacture of such drugs would be subject to FDA's drug

CGMP regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations (CFR), Parts 210 and 211, among other requirements described above.

In addition, you should also correct the violations of FDCA section 502(f)(1) noted above.

D. 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 if you have taken any specific steps 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 the corrective action cannot be completed within 15 working days, state the reason for the delay and the time frame within which the correction will be completed.

Your written notification should be addressed to: FDA Dallas District Office, U.S. Food and Drug Administration, ATTN: Acting District Director, 4040 North Central Expressway, Suite 300, Dallas, Texas 75204.

If you have any questions about the contents of this letter, please contact Chad J. Whitwell, Compliance Officer, at (214) 253-5328.

Sincerely,
/S/
Karlton T. Watson
Acting Dallas District Director

CC:
Lori Woznicki, Food and Drug Inspections Branch Manager
Division of Regulatory Services
Texas Department of State Health Services
1100 E. 49th Street – Mail Code 1987
Austin, Texas 78756

Gay Dodson, RPh, Executive Director
Texas State Board of Pharmacy
William P. Hobby Building
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333 Guadalupe Street
Austin, Texas 78701

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[1] Domperidone was nominated for inclusion on the list of bulk drug substances that can be used in compounding that must be developed through regulation pursuant to section 503A(b)(1)(A)(i)(III) of the FDCA (503A bulks list). 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 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 being 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 sufficient supporting information for FDA to evaluate it, and that it has not been identified by FDA as a substance that appears to present significant safety risks pending further evaluation. Domperidone has been identified as a substance that appears to present significant safety risks. For additional information, see the guidance at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469120.pdf.

[2] For example, section 503A also addresses anticipatory compounding, which includes compounding (not distribution) before receipt of a valid prescription order for an individual patient. We are not addressing anticipatory compounding here.