Maplerose Enterprises, LLC, dba Pencol Pharmacy 8/2/17

U.S. Food and Drug Administration
Division of Pharmaceutical Quality Operations IV
19701 Fairchild Road
Los Angeles, CA 92612

WARNING LETTER

VIA UNITED PARCEL SERVICE
SIGNATURE REQUIRED

August 2, 2017 **CMS# 520095**

Tony E. Jones, Owner
Maple Rose Enterprises, Inc. dba Pencol Compounding Pharmacy
1325 S Colorado Boulevard, Suite B-024
Denver, Colorado 80222-3303

Dear Mr. Jones:

From August 8, 2016, to August 22, 2016, U.S. Food and Drug Administration (FDA) investigators inspected your facility, Maple Rose Enterprises, Inc., dba Pencol Compounding Pharmacy, located at 1325 S Colorado Boulevard, Suite B-024, Denver, Colorado 80222-3303. 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.

FDA issued a Form FDA 483 to your firm on August 22, 2016. FDA acknowledges receipt of your firm's written response, dated September 12, 2016. Based on this

inspection, it appears that you produced drug products that violate the FDCA and your written response does not fully address our concerns as discussed below.

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) ad 355(a)].[1] Receipt of valid prescriptions for individually-identified patients is one of the conditions for the exemptions under section 503A.

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. For example, the investigators noted that your firm did not receive valid prescriptions for individually-identified patients for a portion of the drug products you produced.

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 a non-sterile cleaning and disinfecting agent on the ISO 5 classified work surfaces, and that your sporicidal agent’s contact time was insufficient to ensure efficacy. In addition, investigators observed a gap in the ceiling tile located above of the aseptic production area. The investigators also found that your firm did not perform post-filtration integrity testing of the filter used to sterilize drugs intended to be sterile according to the manufacturer’s recommendation. Also, your firm failed to demonstrate, through appropriate studies, that your hoods are able to provide adequate protection of the ISO 5 areas where sterile products are processed.

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 [21 U.S.C. § 351(a)(2)(B)]. The violations 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 an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions (21 CFR 211.42(c)(10)(v)).
3. Your firm failed to ensure that manufacturing personnel wear clothing appropriate to protect drug products from contamination (21 CFR 211.28(a)).
4. Your firm failed to maintain buildings used in the manufacture, processing, packing or holding of drug products in a good state of repair (21 CFR 211.58).
5. 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 [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.[2] Accordingly, these ineligible drug products are misbranded under section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)]. As previously stated, 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.

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 response to Observation 1 pertaining to the raised ceiling tile, you did not identify or implement any actions to ensure that gaps in ceiling tiles above aseptic processing areas would be addressed.
2. In response to Observation 4 pertaining to disinfectants, you did not indicate whether any sporicidal agent would continue to be used on the surfaces of the ISO 5 production equipment, and have not provided documentation to justify a 10 minute contact time for Spor-Klenz.
3. In response to Observation 4 pertaining to autoclaved beakers, utensils, and stir equipment used in the production of injectables which were inadequately

depyrogenated, your response does not specify the cycle parameters nor does it include any documentation (such as batch records, procedures, and printouts from the **(b)(4)**).

4. In response to Observation 5 pertaining to smoke studies, the videos included in your response were not performed under dynamic conditions as no operators were observed simulating aseptic manipulations.

For more information on compounding, please see FDA's website, at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm.

Please be aware that section 501(a)(2)(A) of the FDCA [21 U.S.C. § 351(a)(2)(A)] concerning insanitary conditions applies regardless of whether drug products you compound meet the conditions of section 503A, including the condition for receipt of a prescription for an identified individual patient prior to compounding and distributing drug products.

As explained above, receipt of valid prescriptions for individually-identified patients is a condition of section 503A, which your firm failed to meet for a portion of the drug products you produced. In addition, we note that between May 2016 and July 2016 you compounded and distributed cisapride products. Drug products compounded using cisapride are not eligible for the exemptions provided by section 503A of the FDCA because cisapride appears on the withdrawn or removed list at 21 CFR §216.24 (effective November 7, 2016). 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 sections 505 and 502(f)(1) of the FDCA [21 U.S.C. §§ 355(a) and 352(f)(1)] and fully implement corrections that meet the minimum requirements of the CGMP regulations.[3]

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 introduce into interstate commerce 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# 520095) and should be sent to:

CDR Steven E. Porter, Jr.
Director, Office of Pharmaceutical Quality Operations, Division IV
Food and Drug Administration
19701 Fairchild Road
Irvine, California 92612

If you have questions regarding drug product issues in this letter, please contact Dr. Dionne via email at Matthew.Dionne@fda.hhs.gov or by phone at 303-236-3064 and reference unique identifier **520095**.

Sincerely,
/S/
Steven E. Porter, Jr.
Director, Office of Pharmaceutical Quality Operations, Division IV

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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] 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).

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