Custom RX LLC dba Custom Rx Pharmacy and Wellness Concepts 10/18/18

Division of Pharmaceutical Quality Operations III
300 River Place, Suite 5900
Detroit, MI 48207
Telephone: (313) 393-8100
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October 18, 2018

WARNING LETTER

Case # 559540

UPS NEXT DAY
SIGNATURE REQUIRED

Jan R. Gerber
Owner/President and CEO
Custom Rx, LLC
dba Custom Rx Pharmacy and Wellness Concepts
3510 N Ridge Road, Suite 900
Wichita, KS 67205-1224

Dear Mr. Gerber:

From July 31, 2017, to August 15, 2017, a U.S. Food and Drug Administration (FDA) investigator inspected your facility, Custom Rx, LLC dba Custom Rx Pharmacy and Wellness Concepts, located at 3510 N Ridge Road, Suite 900 Wichita, KS 67205-1224. During the inspection, the investigator 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 investigator 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 15, 2017. FDA acknowledges receipt of your facility's response, dated August 29, 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 of the FDCA.

In addition, for a compounded drug product to qualify for the exemptions under section 503A of the FDCA, 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 with 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 [21 U.S.C. § 353a(b)(1)(A)(i)]).

B. Failure to Meet the Conditions of Section 503A

During the inspection, the FDA investigator noted that drug products produced by your firm failed to meet the conditions of section 503A of the FDCA. For example, the investigator noted:

1. Your firm did not receive valid prescriptions for individually-identified patients for a portion of the drug products you produced.

2. Your firm compounded drug products using dinitrochlorobenzene or magnesium glycinate. Drug products compounded using dinitrochlorobenzene or magnesium glycinate are not eligible for the exemptions provided by section 503A(a) of the FDCA [21 U.S.C. § 353a(a)], because dinitrochlorobenzene and magnesium glycinate are not the subject of an applicable USP or NF monograph, are not a component of an FDA-approved human drug, and do not appear on the 503A bulks list.[2]

Therefore, you compounded drug products that do not meet the conditions of section 503A of the FDCA and are not eligible for the exemptions in that section from the requirement under section 505 of the FDCA for FDA approval prior to marketing, 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 of the FDCA as the "ineligible drug products."

Specific violations are described below.

C. Violations of the FDCA

Adulterated Drug Products

The FDA investigator 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 investigator noted the following:

1. An employee sanitized their gloves in the near vicinity of open vials within the ISO 5 hood.
2. An improper cleaning agent (household dish detergent) was used to wash glassware used in sterile drug production.
3. Media fills failed to closely simulate aseptic production operations under the most challenging or stressful conditions.

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 investigator 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. The violations included, for example:

1. 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)).
2. Your firm failed to establish 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)).

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.[3] Under sections 505(a) and 301(d) of the FDCA [21 U.S.C. §§ 355(a) and 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

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.[4] 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 therefore violates section 301(a) 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 August 29, 2017, response to the Form FDA 483.

Regarding the insanitary condition observation cited in the Form FDA 483 for poor aseptic practices, your proposed correction appears to be adequate and we intend to confirm this correction during our next inspection of your firm.

Regarding the other insanitary condition observations cited in 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. Specifically;

1. Your response stated that a different cleaning agent is being used to clean all glassware used in the ISO classified areas. However, your response did not specify the name of the new cleaning agent or whether other changes were made on how glassware used in sterile drug production is cleaned.

2. Your response indicated that changes were made on how your cleanroom area is cleaned after 3rd party entry including how this cleaning is documented. However, your response did not provide sufficient information regarding these changes.

3. Your response described the changes made to your media fill procedure to ensure that it is representative of your aseptic drug operations. However, a copy of the revised media fill procedure was not included with this response. Further, your response did not indicate the date by which this new media fill procedure would be implemented.

In addition, FDA conducted a thorough review of the documentation collected during the inspection of your facility and found additional deficiencies with some of your practices and procedures that were not listed on the Form FDA 483. For example:

1. Your firm applies **(b)(4)** to surfaces within your cleanroom area for **(b)(4)**. Based on publicly available efficacy data from the manufacturer, this contact time is not sufficient for the use of **(b)(4)** as a sporicidal agent.

2. The tryptic soy agar (TSA) plates used for surface sampling do not contain neutralizers to inactivate residual disinfectants. Further, the log used to document environmental monitoring results lists one (1) result even though surface sample plates are **(b)(4)**. Therefore, your environmental monitoring program may not provide adequate information on the quality of your cleanroom areas.

3. Your firm uses several outside laboratories to conduct potency testing on some of the sterile drug products produced. However, one of these laboratories uses non-qualified test methods to determine the strength of the sterile drug product. The use of non-qualified potency test methods may not reliably provide valid results, which puts patients at risk.

4. You have not conducted an endotoxin challenge study to demonstrate that your **(b)(4)** oven is capable of achieving the depyrogenation parameter of **(b)(4)** ºC for **(b)(4)** minutes.

5. We also noticed that your firm uses different temperature units to describe sterilization and depyrogenation temperature parameters. For example, the media fill temperature parameter is listed in degrees Fahrenheit (**(b)(4)**ºF) while the temperature parameter for stoppers and for terminally sterilized drug products is listed in degrees Celsius (**(b)(4)**ºC and **(b)(4)**ºC [testosterone lot 06132017@9] respectively). In addition, the depyrogenation temperature is also listed in degrees Celsius (**(b)(4)**ºC). You may want to consider using the same temperature unit to describe the temperature parameters for your sterilization and depyrogenation operations to ensure that the temperature used is lethal to microorganisms and does not damage the materials being processed.

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 of the FDCA, including the condition on receipt of a prescription for an identified individual patient prior to compounding and distributing drug products and 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 of the FDCA, your response to the Form FDA 483 did not include a commitment to cease the compounding of drug products using dinitrochlorobenzene or magnesium glycinate. As noted previously in this letter, drug products compounded using these bulk drug substances are not eligible for the exemptions provided by section 503A(a) of the FDCA because they are not the subjects of an applicable USP or NF monograph, are not components of FDA-approved human drugs, and do not appear on the 503A bulks list. We acknowledge that you informed the investigator during the closeout of the inspection that your firm will cease production of these drugs, but we remind you that the investigator requested that you affirm your commitment in writing.

In addition, as explained above, receipt of valid prescriptions for individually-identified patients is a condition of section 503A of the FDCA, which your firm failed to meet for a portion of the drug products you produced.

Should you continue to compound and distribute drug products that do not meet the conditions of section 503A of the FDCA, the compounding and distribution of such drugs would be subject to the requirement for new drug approval, the requirement to label drug products with adequate directions for use, and the requirement to follow drug CGMP regulations. Before doing so, you must comply with the requirements of section 505 and 502(f)(1) of the FDCA and fully implement corrections that meet the minimum requirements of the CGMP regulations.[5]

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, [21 U.S.C. § 351]. 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) and 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 processing 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 address your reply via email to: ORAPharm3_Responses@fda.hhs.gov.

Attn: Brian D. Garthwaite, Ph.D.
Compliance Officer
U. S. Food and Drug Administration
Division of Pharmaceutical Quality Operations III

Refer to the Warning Letter Number above (Case# 559540) when replying. Please contact Dr. Garthwaite by phone at (612) 758-7132 if you have questions regarding the contents of this letter.

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

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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) of the FDCA 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. Dinitrochlorobenzene, magnesium glycinate, and melatonin were nominated for inclusion on the 503A bulks list; however, they were not nominated with adequate support for FDA to evaluate the substances. For additional information, see the guidance at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469120.pdf (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469120.pdf).
[3] The specific products made by your firm are drugs within the meaning of section 201(g) of the FDCA [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.
[4] 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).
[5] In this letter, we do not address whether your proposed corrective actions would resolve the CGMP violations noted above.

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