Talon Compounding Pharmacy 10/3/17

U.S. FOOD & DRUG ADMINISTRATION

Office of Pharmaceutical Quality Operations, Division II
4040 N. Central Expressway, Suite 300
Dallas, Texas 75204

October 3, 2017

CMS Case # 522630

WARNING LETTER

VIA UPS EXPRESS

Rachel S. Pittman, Pharmacist-In-Charge and Owner
R&R Compounding Pharmacy, LLC
dba Talon Compounding Pharmacy
2950 Thousand Oaks Drive, Suite 25
San Antonio, Texas 78247-3347

Dear Dr. Pittman,

From June 21, 2016 to June 29, 2016, U.S. Food and Drug Administration (FDA) investigators inspected your facility, Talon Compounding Pharmacy, located at 2950 Thousand Oaks Drive, Suite 25, San Antonio, Texas. 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 exemptions 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 June 29, 2016. FDA acknowledges receipt of your facility's response to the Form FDA 483 received on July 22, 2016. Additionally, FDA acknowledges that on July 21, 2016, your firm voluntarily recalled all lots of lyophilized HCG (Human Chorionic Gonadotropin) and sermorelin within expiry due to a lack of sterility assurance. 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 collected evidence demonstrating that drug products produced by your firm failed to meet the conditions of section 503A. For example:

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

2. Your firm compounded drug products using **(b)(4)** are not eligible for the exemptions provided by section 503A(a), because these bulk drug substances are not the subject of an applicable USP or NF monograph, are not components 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 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 observed 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:

1. Your firm transferred **(b)(4)** from an ISO 5 classified work bench to a **(b)(4)** located in the same cleanroom, exposing the sterile drug product within the **(b)(4)** to less than ISO 5 classified air. Furthermore, these **(b)(4)** remained in the **(b)(4)** for at least 4 hours prior to being moved to the **(b)(4)** for further processing.

2. Your firm's cleanroom is separated from an unclassified area by only plastic flap coverings.

3. There are gaps between the ceiling and the HEPA filters and light fixtures in your firm's cleanroom.

4. An operator at your firm was observed performing aseptic manipulations in the ISO 5 classified work area without sanitizing or changing their gloves after retrieving items from below the ISO 5 classified work surface. Another operator was observed using their gloved hand to place **(b)(4)** drug product intended to be sterile. During this process, the operator's gloved hand moved directly over the top of open vials. In addition, while gowning, an operator was observed touching the outside of their gloved hand with their bare hand.

5. Your firm did not use a sporicidal agent to disinfect the ISO 5 classified work bench. In addition, your firm used an expired disinfectant **(b)(4)** in the aseptic processing bench on at least two days.

6. Your firm did not sterilize or depyrogenate in-process glassware or **(b)(4)** used for production of drugs intended to be sterile.

7. Your firm stored open packages of sterilized vials and stoppers, used for production of drug products intended to be sterile, on a rack in the cleanroom without additional protection.

8. Your firm failed to demonstrate through appropriate studies that your work bench in the cleanroom is 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.

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. § 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 response to the Form FDA 483 and your letter of intent to **(b)(4)**. FDA acknowledges that on July 21, 2016, your firm voluntarily recalled all lots of lyophilized HCG and sermorelin within expiry due to lack of sterility assurance.

Regarding the insanitary conditions observed during the inspection, some of your corrective actions appear to be adequate. However, we are unable to fully evaluate the following corrective actions due to a lack of adequate supporting documentation:

1. You did not provide your new protocol for the **(b)(4)** process or supporting documentation to demonstrate how **(b)(4)** will be protected from less than ISO 5 quality air during transfer and while in the **(b)(4)**. In addition, the **(b)(4)** will generate particulates and will not provide an adequate environment to prevent contamination of exposed drug product intended to be sterile.

2. In response to our smoke studies observation, you did not provide a copy of the video or a detailed report describing the conditions of the smoke studies for our review. We remain concerned with the ability of your current work bench design to maintain unidirectional ISO 5 air flow during aseptic production. Furthermore, you indicated that you relocated your **(b)(4)** to the ISO 5 work bench. However, it is unclear whether the updated smoke studies included the **(b)(4)**.

3. In response to our stock solution observation, you did not provide any documentation to support your corrective actions. Further, it is not clear whether your firm will continue to produce drug products intended to be sterile from stock solutions. The storage of solutions over multiple days increases the potential for proliferation, if microbial contamination occurs, and further **(b)(4)** would not remove bacterial endotoxin.

4. Your revised SOP entitled "Cleaning and Disinfection" states that you will use a sporicidal agent **(b)(4)** every **(b)(4)** to disinfect the cleanroom. However, you have not

provided supporting information to demonstrate that the **(b)(4)** frequency is adequate. In addition, the SOP does not indicate whether a sporicidal agent will be used to disinfect the ISO 5 work area.

Conversely, the following corrective actions appear inadequate to address the insanitary conditions noted:

1. You did not provide information on how your operators will put stoppers onto vials of finished drug products intended to be sterile. **(b)(4)** stoppering vials with **(b)(4)** may block first air and could potentially contaminate the drug products.

2. Regarding your response to address the transfer of **(b)(4)** into the ISO 5 area without disinfection, we remain concerned with your current practice because other drug products are aseptically processed in the same area. Disinfection should occur at each transition from areas of lower quality air to areas of higher quality air.

3. You did not address the lack of sterilization and depyrogenation of in-process glassware and **(b)(4)**. Use of non-sterile or non-depyrogenated equipment can introduce or increase endotoxins in the finished drug product.

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 concerning insanitary conditions applies regardless of whether drug products you compound meet the conditions of section 503A, including the condition on receipt of a prescription for an identified individual patient prior to distributing drug products and the condition concerning bulk drug substances. (sections 503A(a) and 503A(b)(1)(A)(i) of the FDCA, respectively).

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. Additionally, your firm compounds drugs using bulk drug substances that are not eligible for use in compounding under section 503A or the policy described in FDA guidance.

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.[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. 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 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.

Your written notification should refer to the Warning Letter Number above (**CMS Case # 522630**).

Please address your reply to John W. Diehl, Acting Director, Compliance Branch, at the FDA address provided. In addition, please submit a signed copy of your response to john.w.diehl@fda.hhs.gov.

If you have questions regarding the contents of this letter, you may contact Mr. Diehl at (214) 253-5288.

Sincerely,
/S/
Monica R. Maxwell
Acting Program Division Director
Office of Pharmaceutical Quality Operations, Division II

CC:

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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. **(b)(4)** were not nominated for inclusion on the 503A bulks list. **(b)(4)** was nominated for inclusion on the 503A bulks list, but 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] 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) [21 U.S.C. 321(p)] of the FDCA 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.