KRS Global Biotechnology, Inc 7/6/15

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Florida District
555 Winderley Place, Suite 200
Maitland, Florida 32751

Telephone: 407-475-4700
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VIA UPS NEXT DAY AIR
w/ DELIVERY CONFIRMATION

WARNING LETTER
FLA-15-27
July 6, 2015

Mr. Riccardo D. Roscetti
President and CEO
KRS Global Biotechnology, Inc.
791 Park of Commerce Blvd., Suite 600
Boca Raton, FL 33487-3633

Dear Mr. Roscetti:

You registered with the U.S. Food and Drug Administration (FDA) as an outsourcing facility under section 503B of the Federal Food, Drug, and Cosmetic Act (FDCA) [21 U.S.C. § 353b][1] on December 15, 2013, and again on January 7, 2015. From March 4, 2014, to March 17, 2014, an FDA investigator inspected your facility, KRS Global Biotechnology, Inc., located at 791 Park of Commerce Blvd, Suite 600, Boca Raton, FL 33487-3633. During the inspection, the investigator observed serious deficiencies in your practices for producing sterile drug products, which put patients at risk. For example, the investigator observed that operators were manually stoppering vials with their gloved hands. In addition, your firm does not perform adequate pressure differential monitoring in the clean room. Furthermore, the investigator observed that environmental monitoring is not conducted daily during operations. Therefore, your products may be produced in an environment that poses a significant contamination risk. In addition, the investigator observed that you failed to meet the conditions under section 503B of the FDCA necessary for drugs produced by an outsourcing facility to qualify for exemptions from certain requirements under the FDCA. FDA issued a Form FDA 483 to your facility on March 17, 2014. FDA acknowledges receipt of

your facility's response, dated March 31, 2014, and an undated letter received by FDA on February 13, 2015.

Based on this inspection, it appears your facility is producing drugs that violate the FDCA.

A. Compounded Drugs under the FDCA

The Drug Quality and Security Act (DQSA) was enacted on November 27, 2013. Title I of the DQSA, the Compounding Quality Act (CQA), added a new section 503B to the FDCA. Under section 503B(b), a compounder can register as an outsourcing facility with FDA. Drug products compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility can qualify for exemptions from the drug approval requirements in section 505 of the FDCA [21 U.S.C. § 355(a)], the requirement in section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)] that labeling bear adequate directions for use and the Drug Supply Chain Security Act requirements in section 582 of the FDCA [21 U.S.C. § 360eee-1] if the conditions in section 503B of the FDCA are met.

An outsourcing facility, which is defined in section 503B(d)(4) of the FDCA [21 U.S.C. § 353b(d)(4)], is a facility at one geographic location or address that — (i) is engaged in the compounding of sterile drugs; (ii) has elected to register as an outsourcing facility; and (iii) complies with all of the requirements of this section. Outsourcing facilities must comply with other provisions of the FDCA, including section 501(a)(2)(B) [21 U.S.C. § 351(a)(2)(B)], regarding current good manufacturing practice (CGMP), and section 501(a)(2)(A) [21 U.S.C. § 351(a)(2)(A)], regarding insanitary conditions. Generally, CGMP requirements for the preparation of drug products are established in Title 21 of the Code of Federal Regulations (CFR) parts 210 and 211.

B. Violations of the FDCA

The investigator noted that drug products that were intended or expected to be sterile were prepared, packed, or held under insanitary conditions whereby they may have been contaminated with filth or rendered injurious to health, causing them to be adulterated within the meaning of section 501(a)(2)(A) of the FDCA. Furthermore, the FDA investigator observed significant CGMP violations at your facility, causing your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA.

In addition, the FDA investigator observed that your facility failed to meet the conditions of section 503B. During the inspection, the FDA investigator noted that some of your facility's drug products do not include the following on the label: the statement "This is a compounded drug," the date the drug was compounded, and storage and handling instructions. Some of your drug products do not list the inactive ingredients, identified by established name and the quantity or proportion of each ingredient, on the drug product label or the container. In addition, some of the drug product containers do not include the following information to facilitate adverse event reporting: **www.fda.gov/medwatch** and 1-800-FDA-1088. [Section 503B(a)(10) of the FDCA [21 U.S.C. § 353b(a)(10)]].

In addition, your facility failed to submit a report to FDA upon initial registration as an outsourcing facility in December 2013 identifying the drug products that you compounded during the previous 6-month period (Section 503B(b)(2) of the FDCA [21 U.S.C. § 353b(b)(2)]).

Because your compounded drug products have not met all of the conditions in section 503B, they are not eligible for the exemptions under section 503B from the FDA approval requirements in section 505, the requirement under section 502(f)(1) that labeling bear adequate directions for use, and the Drug Supply Chain Security Act requirements described in section 582 of the FDCA. **[2]**

Specific violations are described below.

Adulterated Drug Products

The FDA investigator noted that drug products compounded in your facility that were 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, the investigator observed that operators were manually stoppering vials with their gloved hands. In addition, your firm does not perform adequate pressure differential monitoring in the cleanroom. Furthermore, the investigator observed that environmental monitoring is not conducted daily during operations. Therefore, your products may be produced in an environment that poses a significant contamination risk.

The FDA investigator also noted CGMP violations at your facility, causing your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations include, 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 adequately design the facility with adequate separation or defined areas or such other control systems necessary to prevent contamination or mix-ups (21 CFR 211.42(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 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)).

Outsourcing facilities must comply with CGMP requirements under section 501(a)(2)(B) of the FDCA. FDA's regulations regarding CGMP requirements for the preparation of drug products have been established in 21 CFR parts 210 and 211. FDA intends to promulgate more specific CGMP regulations for outsourcing facilities. FDA has issued a draft guidance, *Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act*. This draft guidance, when finalized, will describe FDA's expectations regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 until more specific CGMP regulations for outsourcing facilities are promulgated.

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 your drug products.[3] Under sections 301(d) and 505(a) of the FDCA [21 U.S.C. §§ 331(d) and 355(a)], a new drug may

not be introduced 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.

Misbranded Drug Products

You compound drug products that are intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners, and adequate directions cannot be written for them 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). The introduction or delivery for introduction into interstate commerce of these products therefore violates section 301(a) of the FDCA. 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 misbranded.

Failure to Report Drugs

As noted above, your facility failed to submit a report to FDA upon initial registration as an outsourcing facility in December 2013 identifying the drug products that you compounded during the previous 6-month period (Section 503B(b)(2) of the FDCA [21 U.S.C. § 353b(b)(2)]). The failure to report drugs by an entity that is registered with FDA in accordance with section 503B(b) is a prohibited act under section 301(ccc)(3) of the FDCA [21 U.S.C. § 331(ccc)(3)].

C. Corrective Actions

In your March 31, 2014 letter, and undated letter received by FDA on February 13, 2015, you described certain corrective actions you took in response to the Form FDA 483 observations. You stated that you do not engage in drug manufacturing and reference your purported compliance with United States Pharmacopeia (USP)-National Formulary (NF) General Chapter <797> Pharmaceutical Compounding - Sterile Preparations. You also reference the exemption under section 503A of the FDCA from CGMP requirements in section 501(a)(2)(B). However, in your most recent response, you state that you intend to adhere to CGMP requirements for finished drug products established in 21 CFR parts 210 and 211.

As noted above, your firm registered as an outsourcing facility under section 503B of the FDCA. Section 503B does not provide an exemption from section 501(a)(2)(B) of the FDCA. Outsourcing facilities are subject to CGMP requirements under section 501(a)(2)(B) of the FDCA.

Although several of your proposed corrective actions appear adequate, others are deficient. For example, your written response stated that you would implement the use of biological indicators for the validation of the **(b)(4)** and depyrogenation oven. However, your firm did not commit to validating the terminal sterilization process of your sterile drug products. Additionally, you stated that a procedure will be implemented to use in the determination of filter integrity but your response cannot be adequately evaluated because it did not include the procedure or sufficient detail to describe the filter integrity testing to be performed on the filters you currently use. Also, it is unclear if your firm will continue to manually hand stopper vials. Furthermore, our inspection revealed additional observations that remain as a concern, such as, it is not clear if the “ISO 5 blanket” at the opening of the lyophilizer will prevent exposure of the partially stoppered vials to an area of less clean air (i.e., ISO 7). In your corrective actions you have not indicated that your firm will monitor pressure differentials during operations, nor have you committed to conduct environmental

monitoring of the ISO 5 area daily during operations. Finally, your firm has not shown that the sterility test method routinely used for release is adequate for its intended use.

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. You should fully implement necessary corrections in order to ensure that the drug product(s) produced by your firm conform to the basic quality standards that ensure safety, identity, strength, quality, and purity.

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. FDA intends to re-inspect your facility to verify corrective actions have been completed.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps 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 the corrective actions cannot be completed within fifteen working days, state the reason for the delay and the time frame within which the corrections will be completed. Your written notification should refer to the Warning Letter Number above (FLA-15-27). Please address your reply to Andrea Norwood, Compliance Officer, at the address above.

If you have questions regarding the contents of this letter, please contact Andrea Norwood at 407-475-4724.

Sincerely,
/S/
Susan M. Turcovski
Director, Florida District

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[1] *See* Pub. L. No. 113-54, § 102(a), 127 Stat. 587, 587-588 (2013).

[2] See, e.g., section 503B(a)(11) of the FDCA [21 U.S.C. § 353b(a)(11)].

[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) of the FDCA [21 U.S.C. § 321(p)] because they are not generally recognized as safe and effective for their labeled uses.