Hybrid Pharma, LLC 11/30/18

U.S. FOOD & DRUG ADMINISTRATION

U.S. Food & Drug Administration
Office of Pharmaceutical Quality Operations, Division II
4040 N. Central Expressway, Suite 300
Dallas, Texas 75204
www.fda.gov (http://www.fda.gov)

November 30, 2018

CMS CASE #566443

WARNING LETTER

VIA UPS EXPRESS

Ponswamy Rajalingam, Ph.D.
Owner and President
Hybrid Pharma, LLC
1015 West Newport Center Drive, Suite 106-A
Deerfield Beach, Florida 33442-7707

Dr. Rajalingam:

Your firm 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 January 14, 2015, and again on December 20, 2016. From July 18, 2016 to July 28, 2016, FDA investigators inspected your facility, Hybrid Pharma, LLC, located at 1015 West Newport Center Drive, Suite 106-A, Deerfield Beach, Florida 33442-7707. During the inspection, the investigators noted that drug products you produced failed to meet the conditions of section 503B of the FDCA necessary for drugs produced by an outsourcing facility to qualify for exemptions from certain provisions of the FDCA.

FDA issued a Form FDA 483 to your facility on July 28, 2016. FDA acknowledges receipt of your facility's response, dated August 17, 2016, and your subsequent notification, received on June 12, 2017. Based on this inspection, it appears you produced drugs that violate the FDCA.

A. Compounded Drug Products 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) of the FDCA, 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 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.[2]

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 applicable 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.

For a compounded drug product to qualify for the exemptions under section 503B, bulk drug substances used to compound it must appear on a list established by the Secretary identifying bulk drug substances for which there is a clinical need ("503B bulks list"), or that appear on the drug shortage list in effect under section 506E of the FDCA at the time of compounding, distribution, and dispensing (section 503B(a)(2)(A)(i) of the FDCA [21 U.S.C. § 353b(a)(2)(A)(i)]).

In addition, for a compounded drug product to qualify for the exemptions under section 503B, the labeling of the drug must include certain information (section 503B(a)(10) of the FDCA [21 U.S.C. §353b(a)(10)]).]

Further, for a compounded drug product to qualify for the exemptions under section 503B, it must be compounded in an outsourcing facility that is in compliance with the registration and reporting requirements in section 503B(b) including the requirement to submit a report to FDA upon initially registering as an outsourcing facility, once in June of each year, and once in December of each year identifying the drug products compounded during the previous 6-month period (section 503B(b)(2) of the FDCA [21 U.S.C. §353b(b)(2)]) as well as the requirement to submit adverse event reports to FDA (section 503B(b)(5) of the FDCA [21 U.S.C. §353b(b)(5)]).

B. Failure to Meet the Conditions of Section 503B

During the inspection, FDA investigators noted that drug products produced by your facility failed to meet the conditions of section 503B. For example, the investigators noted:

1. Your facility compounded drug products using sildenafil, human chorionic gonadotropin, and testosterone cypionate. Drug products compounded using these bulk drug substances are not eligible for the exemptions provided by section 503B because they do not appear on the 503B bulks list, and are not used to compound a drug that appears on the drug shortage list.[3]

2. Some of your facility's drug products did not include the following information on the labels: the statements, "This is a compounded drug," "Not for resale," the National Drug Code number, and storage and handling instructions. Additionally, some of your facility's drug products did not include the following information on the container to facilitate adverse event reporting: **www.fda.gov/medwatch (http://www.fda.gov/medwatch)** and 1-800-FDA-1088.

3. Your facility failed to submit a report to FDA upon initially registering as an outsourcing facility, and your firm's subsequent reports submitted to FDA failed to identify all of the drug products that you compounded during the previous 6-month period.

4. Your facility has not developed or implemented written processes for the surveillance, receipt, evaluation, and reporting of adverse events for the drug products it compounds.

Because your compounded drug products have not met all of the conditions of section 503B, they are not eligible for the exemptions from the FDA approval requirements of 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.

Specific violations are described below.

C. Violations of the FDCA

Misbranded Drug Products

You compound drug products that 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 causing them to be misbranded under section 502(f)(1) of the FDCA.[4] The introduction or delivery for introduction into interstate commerce of these products therefore violates section 301(a) of the FDCA.

Failure to Report Drugs

As noted above, your facility failed to submit a report to FDA upon initial registration as an outsourcing facility in January 2015, and your firm's subsequent reports did not identify all of the drug products that you compounded during the previous 6-month period (section 503B(b)(2) of the FDCA). 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)].

D. Corrective Actions

We have reviewed your facility's responses to the Form FDA 483.

Regarding observations related to the conditions of section 503B of the FDCA, your corrective actions to your labels appear to be adequate based upon our review of the revised labels submitted in your Form FDA 483 response, dated August 17, 2016.

As explained above, for a drug product compounded using a bulk drug substance to qualify for exemptions under section 503B, the compounded drug must either (i) be compounded using a bulk drug substance that appears on the 503B bulks list, or (ii) appear on FDA's drug shortage list at the time of compounding, distribution, and dispensing. Your firm failed to meet this condition for a portion of the drug products you produced.

Additionally, for a compounded drug product to qualify for the exemptions under section 503B, it must be compounded in an outsourcing facility that is in compliance with the registration and reporting requirements in section 503B(b). Should you continue to compound and distribute drug products that do not meet the conditions of section 503B, the compounding and distribution of your drugs would be subject to the new drug approval requirement, the requirement to label drug products with adequate directions for use, and the Drug Supply Chain Security Act requirements.

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 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 Case #566443**). Please electronically submit your reply on your firm's letterhead to LCDR John W. Diehl, Director, Compliance Branch, at **john.diehl@fda.hhs.gov (mailto:john.diehl@fda.hhs.gov)** and **ORAPHARM2_Responses@fda.hhs.gov (mailto:ORAPHARM2_Responses@fda.hhs.gov)**.

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

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

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

[2]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 503B of the FDCA.

[3]On June 9, 2016, FDA issued a final guidance titled, *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act*. This guidance describes FDA's interim regulatory policy for outsourcing facilities registered under section 503B of the FDCA while the 503B bulks list is being developed. Specifically, the guidance sets out conditions under which FDA does not intend to take action against an outsourcing facility for compounding a drug product using a bulk drug substance that is not included on the 503B list and does not appear on the drug shortage list in effect under section 506E at the time of compounding, distribution, and dispensing until the substance is identified in a final rule as included or not included on the 503B bulks list. These conditions include that the substance may be eligible for inclusion on the 503B 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. Testosterone cypionate was nominated for inclusion on the 503B bulks list but was not nominated with adequate support for FDA to evaluate the substance. Sildenafil and human chorionic gonadotropin were not nominated for inclusion on the 503B bulks list, nor did they appear on the drug shortage list in effect under section 506E at the time of compounding and distribution. For additional information, see the FDA website for the most recent version of this guidance at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469122.pdf (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469122.pdf)

[4]Your compounded 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).

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