PharmaLogic CSP, Inc. 4/29/16

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Baltimore District
6000 Metro Drive, Suite 101
Baltimore, MD 21215

Via UPS

WARNING LETTER
460851

April 29, 2016

Steve Chilinski, President/CEO
PharmaLogic Holdings Corp.
1 South Ocean Blvd.
Suite 206
Boca Raton, FL 33432

Dear Mr. Chilinski:

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 July 1, 2014, and again on January 5, 2015, and at the time of FDA's inspection from December 8, 2014, to December 12, 2014, your facility, PharmaLogic CSP, Inc., located at 9 W. Benedum Industrial Park Drive, Bridgeport, West Virginia was registered as an outsourcing facility.***2*** Although, as of the date of this letter, your facility is no longer registered as an outsourcing facility, this letter discusses violations identified during the time you were registered as an outsourcing facility. Because you are no longer registered as an outsourcing facility, in the corrective action section, this letter also discusses the conditions a compounded drug product must meet in order to qualify for the exemptions under section 503A of the FDCA [21 U.S.C. § 353a].

During the inspection, the investigators observed serious deficiencies in your practices for producing sterile drug products, which put patients at risk. For example, the investigators observed that **(b)(4)**, is used to make the disinfectants used in the ISO 7 and ISO 8 areas, and no sporicidal agents are used to clean either of these rooms. In addition, no disinfectants or sporicidal agents are used in cleaning the **(b)(4)** ISO 5 hoods used to make sterile drug products and the **(b)(4)** pass-through boxes used to bring supplies into the ISO 7 Cleanroom. Furthermore, a sponge mop

is used to clean the floors, walls, and ceilings in the ISO 7 Cleanroom and ISO 8 Anteroom with non-sterile **(b)(4)**, and the mop is stored in an unclassified area between cleanings for up to a week. Moreover, buckets used to bring **(b)(4)** from an unclassified common area into the ISO 7 Cleanroom are not wiped or sanitized after contacting multiple non-sterile surfaces including the inside of a sink, the floor of the unclassified common area, and the floor of the ISO 8 Anteroom.

In addition, the investigators 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 December 12, 2014. FDA acknowledges receipt of your facility's response, received January 5, 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 50l(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 investigators 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 investigators 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 investigators observed that your facility failed to meet the conditions of section 503B, which applied to your facility at the time of the inspection. For example, during the inspection, FDA investigators noted that some of your facility's drug products do not include the statement "This is a compounded drug" on the label, and none of your facility's drug products include the statement "Office Use Only" and the date the drug was compounded on the label. Additionally, some of your facility's drug products do not include the route of administration on the container. [Section 503B(a)(10) of the FDCA [21 U.S.C. § 353b(a)(10)]].

Because your compounded drug products did not meet all of the conditions in section 503B of the FDCA, they were not eligible for the exemptions under section 503B from the FDA approval requirements in section 505 of the FDCA, the requirement under section 502(f)(l) of the FDCA that labeling bear adequate directions for use, and the Drug Supply Chain Security Act requirements described in section 582 of the FDCA.***3***

Specific violations are described below.

Adulterated Drug Products

FDA investigators 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 investigators observed that **(b)(4)** is used to make the disinfectants used in the ISO 7 and ISO 8 areas, and no sporicidal agents are used to clean either of these rooms. In addition, no disinfectants or sporicidal agents are used in cleaning the **(b)(4)** ISO 5 hoods used to make sterile drug products and the **(b)(4)** pass-through boxes used to bring supplies into the ISO 7 Cleanroom. Furthermore, a sponge mop is used to clean the floors, walls, and ceilings in the ISO 7 Cleanroom and ISO 8 Anteroom with non-sterile **(b)(4)**, and the mop is stored in an unclassified area between cleanings for up to a week. Moreover, buckets used to bring **(b)(4)** from an unclassified common area into the ISO 7 Cleanroom are not wiped or sanitized after contacting multiple non-sterile surfaces including the inside of a sink, the floor of the unclassified common area, and the floor of the ISO 8 Anteroom.

FDA investigators 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 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 an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42 (c)(10)(iv)).
3. 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)).

4. Your firm failed to withhold from use each lot of components, drug product containers, and closures until the lot had been sampled, tested, or examined, as appropriate, and released for use by the quality control unit (21 CFR 211.84(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.

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

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; 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)(l) of the FDCA. As stated above, because your compounded drug products did not meet all of the conditions in section 503B of the FDCA, they were not exempt from the requirements of section 502(f)(l) of the FDCA (see, e.g., 21 CFR 201.115). 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.

C. Corrective Actions

In your January 5, 2015, response to the Form FDA 483 issued to your facility on December 12, 2014, you described certain corrective actions you have taken or are planning to take in response to the Form FDA 483 observations. Corrective actions are necessary to address the insanitary conditions identified at your facility, and should be implemented if you continue to compound sterile drugs, regardless of whether you are registered as an outsourcing facility or you seek to compound drugs in accordance with section 503A of the FDCA. Section 503A of the FDCA does not provide an exemption from section 501(a)(2)(A) concerning producing drugs under insanitary conditions.

Although the corrective actions included in your response to address the objectionable conditions observed at your facility appear adequate, your response is deficient in other respects. Specifically, your response did not indicate which disinfectant and sporicidal agent will be implemented in your cleanroom and ISO 5 hoods. Furthermore, you did not provide details of either your planned training or your written policy for Environmental Monitoring, including air and surface sampling

and personnel monitoring during routine production in your aseptic processing areas. Your response did not indicate appropriate interim actions to address deficiencies until corrections are implemented.

Because your facility is no longer registered as an outsourcing facility, drug products that you produce are no longer eligible to qualify for the exemptions under section 503B of the FDCA. However, they can qualify for the exemptions under section 503A of the FDCA if they are compounded in accordance with all of the conditions of section 503A. Section 503A describes the conditions under which certain compounded human drug products are entitled to exemption from three sections of the FDCA: compliance with CGMP, section 501(a)(2)(B); labeling with adequate directions for use, section 502(f)(l); and FDA approval prior to marketing, section 505 [21 U.S.C. §§ 351(a)(2)(B), 352(f)(1), and 355(a)]. Receipt of valid prescriptions for individually-identified patients is one of the conditions for the exemptions under section 503A. In addition, there are other conditions that must be satisfied to qualify for the exemptions in section 503A of the FDCA.***4***

During the inspection, the investigators noted that you compound and distribute a portion of your drug products without receiving valid prescriptions for identified individual patients. Those drug products would not be eligible for the exemptions under section 503A, and, if the CGMP violations cited above are not corrected, such drugs would be adulterated under section 501(a)(2)(B) of the FDCA. Similarly, those drugs would be misbranded under section 502(f)(l) of the FDCA unless their labeling bears adequate directions for use or they are otherwise exempt from section 502(f)(1) (see, e.g., 21 CFR 201.115). Furthermore, if you continue to produce unapproved new drugs and distribute them in interstate commerce without first receiving prescriptions for individually-identified patients, such drugs would be introduced into interstate commerce in violation of section 505(a) of the FDCA. Drug products that are intended or expected to be sterile would be adulterated under section 501(a)(2)(A) of the FDCA unless the violations noted above are corrected.

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.

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, as amended by the Food and Drug Administration Safety and Innovation Act (Pub.L. 112-144, Title VII, section 711). We note that you have chosen to hire a contract testing laboratory to perform some of the required testing of your finished drug products. 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).]

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 Warning Letter Number 460851. Please address your reply to Ernest F. Bizjak, Compliance Officer, at the address above.

If you have questions regarding the contents of this letter, please contact Mr. Bizjak by email at ernest.bizjak@fda.hhs.gov or by phone at 30 I -796-4081.

Sincerely,
/S/
Evelyn Bonnin
District Director
Baltimore District

CC:
Mr. Jeffery A. Fenerty, R.Ph., Executive Director of Sterile Compounding
PharmaLogic CSP, Inc.
9 W. Benedum Industrial Park Drive
Bridgeport, WV 26330

David E. Potters, Executive Director and General Counsel
West Virginia Board of Pharmacy
2310 Kanawha Blvd E
Charleston, WV 25311

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

2 FDA is aware that PharmaLogic WV, Inc. also operates a nuclear pharmacy at a facility located at this same address. This letter does not address PharmaLogic WV, Inc.'s nuclear pharmacy operations.
3 See, e.g., section 503B(a)(11) of be FDCA [21 U.S.C. § 353b(a)(11)].
4 For example, section 503A also addresses anticipatory compounding, which includes compounding (not distribution) before receipt of a valid prescription order for an individual patient. We are not addressing anticipatory compounding here.