Pharmaceutic Labs, LLC. 5/3/17

New York District
158-15 Liberty Ave
Jamaica, NY 11433

WARNING LETTER NYK-2017-9

May 3, 2017

VIA UNITED PARCEL SERVICE
SIGNATURE REQUIRED

Mr. Ernesto R. Samuel
President and Chief Executive Officer
Pharmaceutic Labs, LLC
15 Walker Way
Albany, NY 12205

Dear Mr. Samuel:

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 March 10, 2014, January 28, 2015, October 6, 2015 and October 22, 2016. From August 31, 2015, to September 23, 2015, an FDA investigator inspected your facility, Pharmaceutic Labs, LLC, located at 15 Walker Way, Albany, NY 12205. 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 your firm did not have an adequate contact time for your sporicidal agent used to disinfect your aseptic processing areas. Specifically, the **(b)(4)** minute contact time for **(b)(4)** appears to be inadequate for sporicidal effect. Furthermore, your firm failed to demonstrate through appropriate studies that your aseptic processing areas are able to provide adequate protection of the ISO 5 areas in which sterile products are processed.

In addition, the investigator observed that the products you prepared 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 September 23, 2015. FDA acknowledges receipt of your facility's response, dated October 13, 2015.

Based on this inspection, it appears your facility is producing drugs that violate the FDCA and the Public Health Service Act (PHS Act).

A. Biological Products

The term "biological product" is defined in section 351(i)(1) of the PHS Act [42 U.S.C. §262(i)(1)] to mean a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

Section 351(a)(1) of the PHS Act [42 U.S.C. §262(a)(1)] prohibits the introduction or delivery for introduction into interstate commerce of any biological product unless "a biological license . . . is in effect for the biological product[.]"

B. 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 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]

FDA interprets the term compounding in section 503B not to include repackaging [21 U.S.C. §353b(d)(1)]. Further, for the purposes of section 503B, a drug, including a sterile drug, does not include a biological product that is subject to licensure under section 351 of the PHS Act.[3]
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. As FDA has explained in guidance, a facility "should *not* register…as an outsourcing facility if the *only* activities conducted at the facility are repackaging, compounding non-sterile drugs, compounding animal drugs, or mixing, diluting, or repackaging biological products subject to licensure under section 351 of the PHS Act, because *none of the products produced at the facility would qualify for the exemptions provided in section 503B.*"[4]

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.

C. Eligibility for the Exemptions in Section 503B

During the inspection, the FDA investigator noted that products produced by your facility were not eligible for the exemptions in section 503B.[5][6] As previously noted, repackaging is not "compounding", and biological products subject to licensure under the PHS Act are not "drugs" within the meaning of section 503B. Accordingly, the biological products that you produced were not eligible for the exemptions in section 503B 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.[7] Specifically, FDA noted that your facility did not meet the statutory definition of an "outsourcing facility" in section 503B(d)(4) of the FDCA because you did not engage in the compounding of sterile drugs. The investigator noted that the only product produced by your firm was repackaged Avastin (bevacizumab), a biological product subject to licensure under section 351 of the Public Health Service (PHS) Act.

Specific violations are described below.

D. Violations of the FDCA and PHS Act

Adulterated Drug Products

The FDA investigator noted that drug products prepared 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 your firm did not have an adequate contact time for your sporicidal agent used to disinfect your aseptic processing areas. Specifically, the **(b)(4)** minute contact time for **(b)(4)** appears to be inadequate for sporicidal effect. Furthermore, your firm failed to demonstrate through appropriate studies that your aseptic processing areas are 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.

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 establish an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions (21 CFR 211.42(c)(10)(v)).

3. 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)).

4. Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity (21 CFR 211.160(b)).

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.

Unlicensed Biological Products

To lawfully market a biological product, an FDA-approved biologics license application (BLA) must be in effect under section 351 of the PHS Act [42 U.S.C. §262]. You did not have any FDA-approved BLAs on file for your products.[8] Therefore, your marketing of these products was in violation of the PHS Act.

Misbranded Drug Products

You prepared 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.

C. Corrective Actions

In your October 13, 2015, response to the Form FDA 483, you described certain corrective actions taken in response to the investigator's observations. Although some of your proposed corrective actions appear to be adequate, others appear to be deficient or could not be fully evaluated. For example, in response to our observation of inadequate sampling, your firm revised your SOP (Quality Control Sample, OP.PL.348, Revision 8) for taking QC samples and now require that **(b)(4)** of samples be taken at the beginning, **(b)(4)** in the middle, and **(b)(4)** at the end of the production. However, the example in your SOP shows that only **(b)(4)** syringes are collected for a batch size of **(b)(4)**. As these samples are used for sterility testing

as well as other testing, your sample size appears to be less than what is recommended by USP <71> for parenteral drug products.

Additionally, in response to our observation of inadequate visual inspection, your firm purchased a light box for visual inspection of pooled drug solution and final drug products. However, it is not clear from your response if the visual inspection results will be documented in the batch records.

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 products produced by your firm conform to the basic quality standards regarding 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).]

Finally, we note that, based on your report submitted to FDA in December 2016, identifying the drug products that you prepared during the previous 6-month period, it appears that your facility only engaged in the compounding of non-sterile drug products during that timeframe. As stated above, to meet the definition of "outsourcing facility" in section 503B of the FDCA, a facility must be "engaged in the compounding of sterile drugs" and must comply "with all of the requirements of" section 503B, among other things. Furthermore, the conditions of 503B that must be met for a drug to qualify for the exemptions in that section include that the drug be compounded in an outsourcing facility.[9] Therefore, if an entity registered as an outsourcing facility *only* compounds non-sterile drugs, the entity does not meet the statutory definition of an outsourcing facility, and drugs compounded by it would not qualify for the exemptions in section 503B.[10] In addition, section 503B does not provide exemptions from requirements of the FD&C Act for repackaged drugs, or for biological products that are subject to licensure under section 351 of the PHS Act. An entity that *only* repackages biological products does not meet the statutory definition of an outsourcing facility.

To meet the statutory definition of an outsourcing facility, you would need to, among other things, engage in the compounding of sterile drugs. If you compound sterile drugs in accordance with the conditions of section 503B, those drugs, as well as any

non-sterile drugs that you compound in accordance with the conditions of section 503B, would qualify for the exemptions in section 503B.

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 (NYK-2017-9). Please address your reply to CDR Frank Verni, Compliance Officer, at the address above.

If you have questions regarding the contents of this letter, please contact CDR Verni at (718) 662-5702.

Sincerely,
/S/
Ronald Pace
District Director
New York District

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

[2] *See* Section 503B(a) of the FDCA [21 U.S.C. § 353b(a)].

[3] Although the products produced by your facility are not “drugs” for the purposes of section 503B, as discussed *infra* they are drugs for the purposes of other sections of the FDCA.

[4] See “Guidance for Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act” (August 2015), at 4, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM434171.pdf.

[5] See section 503B(a) of the FDCA [21 U.S.C. §353b(a)].

[6] In January 2017, FDA published Revision 1 to the Draft Guidance: Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application, *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM434176.pdf. That draft guidance, when finalized, will describe the conditions under which FDA does not intend to take action for violations of section 351 of the PHS Act and violations of section 502(f)(1) of the FDCA when a state-licensed pharmacy, a Federal facility, or an outsourcing facility repackages certain biological products, such as Avastin, outside the scope of an approved biologics license application.

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

[8] 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. Finally, they are biological products within the meaning of the PHS Act.

[9] See, e.g., section 503B(a)(11) of the FDCA.

[10] See *id*.