College Pharmacy Incorporated 8/15/16

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Denver District Office
Bldg. 20-Denver Federal Center
P.O. Box 25087
6th Avenue & Kipling Street
Denver, Colorado 80225-0087
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CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER

August 15, 2016

Jerry S. Gillick
Pharmacy Manager/President/Owner
College Pharmacy
3505 Austin Bluffs, Suite 101
Colorado Springs, CO 80918

Ref. #:DEN-16-14-WL

Dear Mr. Gillick:

From May 11, 2015, to May 28, 2015, U.S. Food and Drug Administration (FDA) investigators conducted an inspection of your facility, College Pharmacy, located at 3505 Austin Bluffs, Suite 101, Colorado Springs, CO 80918. FDA investigators previously inspected this facility from March 5, 2013 to March 15, 2013.

During both the 2013 and 2015 inspections, the investigators noted that you were not receiving valid prescriptions for individually-identified patients for a portion of the drug products you were producing. In addition, in both instances the investigators observed serious deficiencies in your practices for producing sterile drug products,

which put patients at risk. For example, during the 2015 inspection our investigators noted that non-sterile cleaning wipes were used to apply disinfectants to the ISO 5 work surfaces and that a portion of your lyophilization operations were not conducted under ISO 5 conditions. Additionally, during the 2015 inspection investigators observed that your firm failed to demonstrate through appropriate studies that your hoods 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.

FDA issued a Form FDA 483 to your firm on May 28, 2015. FDA acknowledges receipt of your firm's responses to the Form FDA 483, dated June 17, 2015, and July 21, 2015.

During the March 2013 inspection, FDA observed that your aseptic processing area where you manipulate sterile drugs was not adequately designed and maintained and posed a risk to the sterile drug products produced by your firm. We also observed poor aseptic practices by employees, which also had the potential to contaminate the sterile drug products produced by your firm. FDA issued a Form FDA 483 to your firm on March 15, 2013. In your April 5, 2013 response to that Form FDA-483, your firm outlined corrections you planned to take to address these inspectional findings. During the 2015 inspection, FDA investigators noted that while your firm made improvements to your aseptic processing area, objectionable conditions regarding your aseptic processing operations remain. In addition, as noted above, you still are not obtaining valid prescriptions for individually-identified patients for a portion of the drug products produced by your firm.[1]

Based on these inspections, it appears that you are producing drugs that violate the Federal Food, Drug, and Cosmetic Act (FDCA). In addition, as explained below, it appears that you are producing biological products that violate the Public Health Service Act (PHS Act).

A. Compounded Drugs Under the FDCA

Section 503A of the FDCA [21 U.S.C. § 353a] describes the conditions under which certain compounded human drug products qualify for exemptions from three sections of the FDCA: compliance with current good manufacturing practice (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)]. Receipt of valid prescriptions for individually-identified patients is one of the conditions that must be met for drug products to qualify for the exemptions under section 503A. During the FDA inspections, the investigators observed that your firm does not receive valid prescriptions for individually-identified patients for a portion of the drug products you produce.[2] Accordingly, the drugs you compound without valid prescriptions for individually identified patients are not entitled to the exemptions in section 503A.

In addition, we remind you that there are a number of other conditions that must be satisfied to qualify for the exemptions in section 503A of the FDCA.[3]

B. Allergenic Products

The FDA investigators also observed that your firm manufactures and markets allergenic products, which are biological products subject to licensure under section 351 of the PHS Act [42 U.S.C. § 262]. 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. [emphasis added]

You use unlicensed materials (rather than FDA-licensed allergenic extracts and appropriate diluents) in manufacturing certain allergenic products. Your manufacture and marketing of those allergenic products is outside the scope of an approved biologics license application.

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 biologics license . . . is in effect for the biological product[.]".

Although section 503A of the FDCA provides an exemption for certain compounded drugs from the requirement to obtain premarket approval under section 505 of the FDCA, it does not provide an exemption from the requirement to obtain premarket approval under section 351 of the PHS Act. Thus, for purposes of section 503A, a "drug" does not include any biological product that is subject to licensure under section 351 of the PHS Act. Accordingly, such biological products are not eligible for the exemptions for compounded drugs under section 503A of the FDCA.[4]

C. Violations of the FDCA and the PHS Act

The drug products and allergenic products that you manufacture and distribute without valid prescriptions for individually-identified patients are misbranded drugs in violation of section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)].

In addition, drug products, including biological products, that are intended or expected to be sterile were prepared, packed, or held under insanitary conditions whereby they may have been contaminated with filth, or whereby they may have been rendered injurious to health, causing them to be adulterated within the meaning of section 501(a)(2)(A) of the FDCA [21 U.S.C. § 351(a)(2)(A)]. Furthermore, because you manufacture and distribute a portion of your drugs without valid prescriptions for individually-identified patients, the manufacture of such drugs is subject to FDA's CGMP regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations (CFR), Parts 210 and 211. Your preparation of biological products is also subject to the CGMP regulations for Finished Pharmaceuticals as well as applicable biological product standards in Title 21, CFR Parts 600-680. The FDA investigators observed significant CGMP violations at your facility, causing such drug products, including allergenic products, to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA.

Unlicensed Biological Products

To lawfully market a biological product, including an allergenic product, a valid biologics license must be in effect under section 351(a) of the PHS Act [42 U.S.C. § 262(a)]. Your allergenic products are not the subject of an approved BLA. Therefore, your marketing of these allergenic products is in violation of the PHS Act.

Section 351(j) of the PHSA [42 U.S.C. § 262(j)] provides that the FDCA, including section 505 of the FDCA, applies to biological products subject to regulation under the PHSA for which BLAs have not been approved. You do not have any FDA approved applications on file for your allergenic products. Under sections 505(a) and 301(d) of the FDCA, 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. Your marketing of these allergenic products without approved applications violates these provisions of the FDCA.

Misbranded Drug Products

The drug products that you compound without obtaining valid prescriptions for individually-identified patients, and the allergenic products that you manufacture without obtaining valid prescriptions for individually-identified patients, 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, and they are not exempt from the requirement to have labeling with adequate directions for use, either under section 502(f)(1) of the FDCA or FDA regulations [*see, e.g.*, 21 CFR § 201.115]. Therefore, these products are misbranded under section 502(f)(1) of the FDCA.

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, including a biological product, that is misbranded, 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, including a biological product, if such act is done while the drug is held for sale after shipment in interstate commerce and results in the drug being misbranded.

Adulterated Drug Products

Additionally, FDA investigators observed that drug products, including biological products, 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 them to be adulterated under section 501(a)(2)(A) of the FDCA. For example, during the 2013 and 2015 inspections, our investigators found that non-sterile agents were utilized in cleaning the ISO 5 work surfaces and that a portion of your lyophilization operations were not conducted under ISO 5 conditions. Additionally, during the 2013 and 2015 inspection, our investigators noted that your firm failed to demonstrate through appropriate studies that your hoods 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.

During the 2013 and 2015 inspections, the investigators also observed CGMP violations at your facility, causing the allergenic products you manufacture and the drug products for which you have not obtained valid prescriptions for individually-identified patients to be adulterated under section 501(a)(2)(B) of the FDCA. The violations observed during our inspections of your facility included, but are not limited to:

1. Your firm failed to validate the procedures used in your aseptic and sterilization operations. (21 CFR 211.113(b))

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

4. Your firm failed to ensure that manufacturing personnel wear clothing appropriate to protect drug product from contamination. (21 CFR 211.28(a))

5. Your firm failed to withhold components from use until the lot has been sampled, tested, examined and released by the quality control unit. (21 CFR 211.84(a))

Under section 301(a) of the FDCA, the introduction or delivery for introduction into interstate commerce of any drug, including a biological product, that is adulterated is a prohibited act. Further, it is a prohibited act under section 301(k) of the FDCA to do any act with respect to a drug, including a biological product, if such act is done while the drug is held for sale after shipment in interstate commerce and results in the drug being adulterated.

D. Corrective Actions

We have reviewed your June 17, 2015, and July 21, 2015, responses to the Form FDA 483 dated May 28, 2015. Although some of your corrective actions appear adequate, others are deficient or cannot be fully evaluated because of insufficient supporting documentation. For example, your responses did not clearly state whether you intended to use sterile wipes to clean and disinfect the ISO 5 work surfaces. Additionally, your responses did not provide sufficient information on when the proposed corrections to your lyophilization operations would be completed and whether interim measures would be taken during the implementation of this correction. Your responses also did not include documentation to show that smoke studies were conducted under dynamic conditions. Further, your responses did not address why your gowning practice did not conform to your gowning procedure requirement of “no exposed skin on extremities” and did not specify when sterile coveralls and hoods would be implemented into your production process. Finally, although you have committed to identifying all microorganisms recovered during environmental monitoring, you have not provided copies demonstrating revision to your applicable written procedures to include establishing appropriate action limits or changes to monitoring frequencies applicable to that of aseptic processing.

Your responses referenced your purported compliance with the United States Pharmacopeia (USP)-National Formulary (NF) General Chapter <797> Pharmaceutical Compounding-Sterile Preparations. However, as discussed above, your firm has manufactured and distributed drugs without valid prescriptions for individually-identified patients, and the manufacture of such drugs is subject to FDA's finished drug product CGMP regulations, 21 CFR parts 210 and 211.

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.

In addition to the issues discussed above, you should note that, for purposes of section 501(a)(2)(B) of the FDCA, CGMP includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, 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 your compounded drug products are neither adulterated nor misbranded. *See* 21 CFR 210.1(b), 21 CFR 200.10(b).

Furthermore, you should also correct the violations of sections 501(a)(2)(A) and 502(f)(1) of the FDCA, and section 351(a) of the PHS Act, noted above.

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 working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct the 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 or PHS Act, include your reasoning and any supporting information for our consideration. If you cannot complete corrective

actions within 15 working days, state the reason for the delay and the time within which you will complete the correction.

Your written response should be sent to U.S. Food and Drug Administration, P.O. Box 25087, Denver, Colorado 80225-0087, Attention: Matthew R. Dionne, Compliance Officer. If you have questions regarding drug product issues in this letter, please contact Dr. Dionne via email at Matthew.Dionne@fda.hhs.gov or by phone at 303-236-3064.

Sincerely,
/S/
LaTonya M. Mitchell
District Director
Denver District

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[1] At the time FDA inspected your facility in 2013, there were conflicting judicial decisions regarding the applicability of section 503A of the FDCA [21 United States Code (USC) 353a], which exempts compounded drugs from several key statutory requirements if certain conditions are met. *Compare Western States Med. Ctr. v. Shalala*, 238 F.3d 1090 (9th Cir. 2001) with *Medical Ctr. Pharm. v. Mukasey*, 536 F.3d 383 (5th Cir. 2008). Nevertheless, receipt of valid prescriptions for individually-identified patients prior to distribution of compounded drugs was relevant for both section 503A of the FDCA and the Agency's Compliance Policy Guide 460.200 (CPG) (2002), which was then in effect. Subsequent to FDA's 2013 inspection of your facility, Congress enacted and the President signed into law the Compounding Quality Act (CQA), which amended FDCA section 503A by eliminating the advertising restrictions that had been the basis for conflicting judicial decisions. The CQA otherwise left section 503A intact, and so clarified that the remainder of section 503A, including the requirement of valid prescriptions for individually-identified patients, is applicable in every federal judicial circuit. Accordingly, the drugs you compound without valid prescriptions for individually-identified patients are not entitled to the exemptions in section 503A.

[2] In your response to the Form FDA 483 dated July 21, 2015, you state that your firm "fills **(b)(4)** or more of its prescriptions for individually[-]identified patients pursuant to a valid prescription from a prescriber, as required by Section 503A," but "[t]he remaining **(b)(4)** or less of medications College Pharmacy compounds are for **(b)(4)**." The condition of section 503A concerning receipt of valid prescriptions for individually-identified patients does not differentiate between in-state and out-of-state patients. This condition applies to all compounded drug products irrespective of interstate shipment.

[3] 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.

[4] In February 2015, FDA published for public comment a draft guidance, *Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application*. Among other things, this draft guidance describes FDA's proposed policies regarding the preparation of "prescription sets" of FDA-licensed allergenic extracts by State-licensed pharmacies, Federal facilities, outsourcing facilities, and physicians. The draft guidance states, in part, that FDA does not intend to take action for violations of section 351 of the PHS Act or sections 502(f)(1) or 501(a)(2)(B) of the FDCA if the prescription sets are prepared by a State-licensed pharmacy, Federal facility, or physician in accordance with certain conditions and applicable requirements. One of these

conditions is that the prescription set be prepared from FDA-licensed allergenic extracts and appropriate diluents; as explained in this letter, allergenic extracts from which your firm manufactures its allergenic products are not the subject of approved biologics license applications.