DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Sidney M. Wolfe, M.D.
Director
Public Citizen's Health Research Group
1600 20th St., NW
Washington, DC 20009

Dear Dr. Wolfe:

Thank you for your letter dated April 22, 2013, expressing concerns about the length of time that passed between the Food and Drug Administration's (FDA or Agency) inspection of Axium Healthcare Pharmacy, dba Balanced Solutions Compounding (Axium) and the firm's subsequent, voluntary recall of all sterile drugs. As you are aware, FDA conducted its inspection of Axium from March 12 to 15, 2013. During the inspection, on March 14, 2013, Axium recalled two lots of contaminated drug products. On April 17, 2013, Axium announced that it was conducting a nationwide recall of all sterile drugs produced at the firm's facility.

We regret that we are unable to comment on this matter at this time because FDA's investigation remains open. However, we direct your attention to publicly-available materials regarding the inspection, including the Agency's July 16, 2013 Warning Letter to Axium (attached), which may address many of the questions raised in your letter. As set forth in the attached Warning Letter, Axium informed FDA that it ceased production of sterile products on March 15, 2013 – the final day of FDA's inspection.

While I cannot specifically address your questions due to the status of FDA's investigation, it may be helpful to note a few items as a general matter. First, FDA does not have authority to require drug recalls. In our experience, drug recalls often involve extended discussions with the firm about FDA's concerns before the firm decides to conduct a voluntary recall and determines the scope of that recall. Second, FDA's testing for microbiological contamination takes a number of days due to the time required for incubated samples to exhibit microbial growth. Finally, following an inspection, FDA experts perform a thorough evaluation of the observations made and evidence collected during the inspection, which may extend beyond those observations cited by the investigators on the FDA Form 483. Based on this review, FDA takes appropriate action, which may include engaging with a firm about remedial actions, such as by conducting or expanding a voluntary recall, or a voluntary shutdown.

I hope that this letter and the FDA Warning Letter dated July 16, 2013, adequately address some of the questions you raised in your April 22 letter.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Florida District
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Maitland, Florida 32751

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

WARNING LETTER

FLA-13-26

July 16, 2013

Mark C. Montgomery
President and CEO
Axium Healthcare Pharmacy, Inc.
dba Balanced Solutions Compounding Pharmacy
550 Technology Park, Suite 1008
Lake Mary, FL 32746-7131

Dear Mr. Montgomery:

From March 12, 2013, to March 15, 2013, U.S. Food and Drug Administration (FDA) investigators conducted an inspection of your facility, Axium Healthcare Pharmacy, dba Balanced Solutions Compounding, located at 550 Technology Park, Suite 1008, Lake Mary, FL 32746-7131. During the inspection, the investigators noted that you were not receiving valid prescriptions for individually-identified patients for a significant number of the drug products you were producing. In addition, the investigators observed serious deficiencies in your practices for producing sterile drug products, which put patients at risk. Two lots of contaminated products were recalled as a result of these observations. These observations and others were noted on an FDA Form 483 issued on March 15, 2013.

During a teleconference with your firm on April 15, 2013, among other things, we notified you that Chromium Chloride Injection 4 mcg/ml, lot # 01182013@9, that was tested for sterility by the FDA laboratory was found to have microbial contamination, and discussed our concerns related to the observed black particles in distributed vials of Triamcinolone Acetonide 60 mg/ml, lot # 01152013@12. In addition, we expressed our concerns regarding the design of your firm's aseptic processing areas and personnel practices, which place sterile products at considerable risk of microbial contamination. During the inspection, we found that your firm does not use a unidirectional flow hood to perform aseptic processing, but instead uses an unprotected metal table with only about 50 percent HEPA filter coverage over it to perform aseptic processing. Your technicians were also observed wearing non-sterile gowns exposing bare skin, extending their arms over sterile uncovered vials, and failing to move in a measured, slow or deliberate manner in the aseptic processing area.

Based on this inspection, it appears that you are producing drugs that do not fall within the exemptions for compounded drugs described in section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA) or within the agency's exercise of enforcement discretion set forth in Compliance Policy Guide 460.200 on Pharmacy Compounding (CPG) (2002).[1]

A. Compounded Drugs Under the FDCA

Currently, there are conflicting judicial decisions regarding the applicability of section 503A of the FDCA [21 U.S.C. § 353a], which exempts compounded drugs from several key statutory requirements if certain conditions are met.[2] Nevertheless, receipt of valid prescriptions for individually-identified patients prior to distribution of compounded drugs is relevant for both section 503A of the FDCA and the agency's CPG. During the FDA inspection, investigators observed that your firm does not receive valid prescriptions for individually-identified patients for a significant number of the drug products you produce. Based on this factor alone, those drugs are not entitled to the statutory exemptions for compounded drugs described in section 503A of the FDCA and do not qualify for the agency's exercise of enforcement discretion set forth in the CPG.[3] In addition, we remind you that there are other conditions that must be satisfied to qualify for the exemptions in section 503A of the FDCA, as well as other factors that FDA considers in determining whether to exercise enforcement discretion under the CPG.[4]

B. Violations of the FDCA

Because the drug products that you manufacture and distribute without valid prescriptions for individually-identified patients are not the subject of approved applications, they are unapproved new drugs and misbranded drugs in violation of sections 505(a) and 502(f)(1) [21 U.S.C. §§ 355(a) and 352(f)(1)] of the FDCA, respectively. In addition, your sterile drug products are 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. As such, all sterile products you manufacture are adulterated within the meaning of section 501(a)(2)(A) [21 U.S.C. § 351(a)(2)(A)] of the FDCA. Furthermore, because you manufacture and distribute drugs

[1] The CPG sets forth a non-exhaustive list of factors that FDA considers in determining whether to take enforcement action when the scope and nature of a pharmacy's activities raise concerns. The CPG is available at: http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074398.htm.

[2] *Compare Western States Med. Ctr. v. Shalala*, 238 F.3d 1090 (9th Cir. 2001) (holding that the solicitation and advertising prohibitions in section 503A are an impermissible regulation of commercial speech and that those provisions are unconstitutional and cannot be severed from the rest of section 503A, causing all of section 503A to be invalid); *with Medical Ctr. Pharm. v. Mukasey*, 536 F.3d 383 (5th Cir. 2008) (compounded drugs are "new drugs" and "new animal drugs" within the meaning of the FDCA and therefore are subject to regulation by the FDA, and the advertising prohibitions in section 503A previously found to be unconstitutional can be severed from section 503A, leaving the remaining parts of that section valid and effective).

[3] *See* 21 U.S.C. § 353a(a) (granting compounded drugs statutory exemptions if, among other things, "the drug product is compounded for an identified individual patient based on the . . . receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient . . . ."); CPG at 2 ("FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of human drugs upon receipt of a valid prescription for an individually-identified patient from a licensed practitioner. This traditional activity is not the subject of this guidance.").

[4] For example, section 503A and the CPG also address 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 because you fail to obtain valid prescriptions for individually-identified patients at any time prior to distribution of a significant number of drugs you produce.

without valid prescriptions for individually-identified patients, the manufacture of those drugs are also subject to FDA's Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations (CFR), Parts 210 and 211. FDA investigators observed significant CGMP violations at your facility, causing such drug product(s) to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA [21 U.S.C. § 351(a)(2)(B)].

Unapproved New Drug Products

You do not have any FDA-approved applications on file for the drug products for which you have not obtained valid prescriptions for individually-identified patients.[5] 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 into or delivered for introduction into interstate commerce unless an application approved by FDA under section 505 of the FDCA [21 U.S.C. § 355] is in effect for the drug. Your marketing of these products, or other applicable products, without an approved application violates these provisions of the FDCA.

Misbranded Drug Products

Additionally, because the drug products for which you have not obtained 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, 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 [21 U.S.C. § 352(f)(1)], and they are not exempt from the requirements of section 502(f)(1) of the FDCA (*see, e.g.*, 21 C.F.R. § 201.115). The introduction or delivery for introduction into interstate commerce of these products therefore violates sections 301(a) of the FDCA [21 U.S.C. § 331(a)].

Adulteration Charges

Additionally, FDA investigators noted that your sterile drug products 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 [21 U.S.C. § 351(a)(2)(A)]. The conditions include that your technicians were also observed wearing non-sterile gowns exposing bare skin, extending their arms over sterile uncovered vials, and failing to move in a measured, slow or deliberate manner in the aseptic processing area. In addition, your firm does not use a unidirectional flow hood to perform aseptic processing, but instead uses an unprotected metal table with only about 50 percent HEPA filter coverage over it to perform aseptic processing.

FDA investigators also noted CGMP violations at your facility, causing the drug products for which you have not obtained valid prescriptions for individually-identified patients to be

[5] 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. 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.

adulterated under section 501(a)(2)(B) of the FDCA [21 U.S.C. § 351(a)(2)(B)]. The violations include, for example:

1. Your firm has failed to reject drug products that did not meet established standards or specifications (21 CFR 211.165(f)).

2. Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements (21 CFR 211.67(a)).

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

4. 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)).

5. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

6. 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)).

7. Your firm failed to ensure that its drug product bore an expiration date that was supported by appropriate stability testing (21 CFR 211.137(a)).

C. Corrective Actions

During a telephone conversation on March 29, 2013, the General Manager of your firm indicated to FDA that your firm ceased production of sterile products on March 15, 2013. In your response to the FDA-483 received on April 10, 2013, you indicated that you suspended production of all sterile products and described several corrective actions. In a letter dated April 16, 2013, you reaffirmed your commitment to cease production of all sterile products, and you indicated that if you decided to resume sterile operations, you would hire a "quality consultant" to help your firm consistently produce drugs of acceptable quality and improve your quality system. In a letter dated May 17, 2013, you notified FDA that your firm intends to exit the compounding business within the next sixty days.

FDA strongly recommends that if you decide to resume production of sterile drugs, 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. In your response to the FDA-483, you referenced your purported compliance with United States Pharmacopeia (USP)-National Formulary (NF) General Chapter <797> Pharmaceutical Compounding-- Sterile Preparations. As noted above, your firm has manufactured and distributed a significant number of drugs without valid prescriptions for individually-identified patients, and the manufacture of such

drugs is subject to FDA's drug CGMP regulations, 21 CFR Parts 210 and 211. Before resuming such operations, you should fully implement corrections that meet the minimum requirements of 21 CFR Part 211 in order to provide assurance 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

Please note that 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 assure that your firm complies with all requirements of federal law and FDA regulations.

If you decide to resume operations, you must 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. Other federal agencies may take this Warning Letter into account when considering the award of contracts.

In addition to taking appropriate corrective actions, you should notify this office prior to resuming production of any sterile drugs. Your notification should be addressed to:Andrea Norwood, Compliance Officer, FDA Florida District Office, U.S. Food and Drug Administration, 555 Winderley Place, Suite 200, Maitland, FL 32751. If you have questions regarding any issues in this letter, please contact our office at 407-475-4700.

Sincerely,

Emma R. Singleton
District Director

Cc: David B. Dillion, CEO
The Kroger Corporation
1014 Vine St,
Cincinnati, OH 45202