Inspections, Compliance, Enforcement, and Criminal Investigations

The Compounding Shop, Inc. 8/12/14

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Florida District
555 Winderley Place, Suite 200
Maitland, Florida 32751

Telephone: 407-475-4700
FAX: 407-475-4770

VIA UPS NEXT DAY AIR
w/ DELIVERY CONFIRMATION

WARNING LETTER
FLA-14-22
August 12, 2014

Dr. Michael S. Haulsee, Pharm.D.
Owner/President
The Compounding Shop, Inc.
4000 Park St. N
St. Petersburg, FL 33709-4034

Dear Dr. Michael S. Haulsee:

From March 18, 2013, to March 22, 2013, and August 23, 2013 to September 3, 2013, U.S. Food and Drug Administration (FDA) investigators conducted inspections of your facility, The Compounding Shop, Inc., located at 4000 Park St. N, St. Petersburg, FL 33709-4034. During the March 2013 inspection, the investigators noted that you were not receiving valid prescriptions for individually-identified patients for a portion of the drug products you were producing. Investigators also noted that your firm continues to make domperidone drug products, despite having received prior warnings regarding this practice in an Untitled Letter issued on March 17, 2005, and a second letter dated May 3, 2005. Domperidone is not the subject of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, nor is it a component of an FDA-approved human drug product, nor does it appear on a list developed by the Secretary under section 503A(b)(1)(A)(i)(III) of the Federal Food, Drug, and Cosmetic Act (FDCA) [21 U.S.C. § 353a]. In addition, the investigators observed serious deficiencies in your practices for producing sterile drug products, which put patients at risk. For example, facility-dedicated clothing, which aseptic technicians wear under reusable sterile gowns, was stored on an open shelf a few feet from the toilet in your restroom. We also observed your personnel placing materials in an ISO 5 hood without disinfecting them, moving directly over open vials and syringes, stoppering by hand instead of using sterile tools or equipment, and using non-sterile wipes and non-sterile blue mats in an ISO 5 hood. These practices expose your drugs to unacceptable contamination hazards. Furthermore, your firm does not test intrathecal drug products for endotoxins and assigns extended beyond use dates to sterile drug products without adequate supporting data.

These observations and others were noted on a Form FDA 483 issued on March 25, 2013. You informed FDA that your firm ceased sterile operations on May 3, 2013. In addition, as a result of FDA's observations, on May 6, 2013 you recalled 660 vials of products that lacked sterility assurance. We acknowledge receipt of your firm's response, dated July 3, 2013, to the Form FDA-483 issued on March 25, 2013. In addition, on September 3, 2013, at the conclusion of the August/September 2013 inspection a Form FDA 483 was issued to your firm. Based on these inspections, it appears that you are producing drugs that violate the Federal Food, Drug, and Cosmetic Act (FDCA).

A. Compounded Drugs Under the FDCA

At the time FDA inspected your facility, there were 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.[1] 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 on Pharmacy Compounding (CPG) (2002), which was then in effect.[2] During the FDA inspection, investigators observed that your firm does not receive valid prescriptions for individually-identified patients for a portion of the drug products you produce. Based on this factor alone, those drugs were not entitled to the statutory exemptions for compounded drugs described in section 503A of the FDCA and did not qualify for the agency's exercise of enforcement discretion set forth in the CPG.[3]

In addition, under the CPG, when determining whether to initiate enforcement action, FDA considered whether a firm compounded finished drugs from bulk active ingredients that were not components of FDA-approved drugs without an FDA sanctioned investigational new drug application. Because domperidone was not a component of an FDA-approved human drug, your compounded drugs containing domperidone would not qualify for the exercise of enforcement discretion set forth in the CPG. Further, the exemptions provided by section 503A(a) did not apply to compounded drug products containing domperidone because domperidone was not the subject of an applicable USP or NF monograph, was not a component of an FDA-approved human drug under section 503A(b)(1)(A)(i) of the FDCA, and it did not appear on a list of bulk drug substances developed by the Secretary under section 503(b)(1)(A)(i)(III).

Since FDA inspected your facility, Congress enacted and the President signed into law the Compounding Quality Act (CQA)[4], 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 is applicable in every federal judicial circuit, including the requirement of valid prescriptions for individually identified patients and the requirement to only compound drug products using bulk drug substances if each bulk drug substance is the subject of an applicable USP or NF monograph, is a component of an FDA-approved human drug, or appears on a list developed by the Secretary under section 503A(b)(1)(A)(i)(III). Accordingly, the drugs you compound without valid prescriptions for individually identified patients and any drug products you compound using domperidone, which is not the subject of an applicable USP or NF monograph, not a component of an FDA-approved human drug, and did not appear on a list developed by the Secretary under section 503A(b)(1)(A)(i)(III), are not entitled to the exemptions in section 503A.[5]

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.[6]

B. Violations of the FDCA

The domperidone drug products and the drug 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)] and your budesonide product was misbranded in violation of section 502(a) of the FDCA [21 U.S.C. § 352(a)].

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 without valid prescriptions for individually-identified patients and also domperidone drug products (which, as noted above, are not eligible for the exemptions provided by section 503A(a)), the manufacture of such drugs is 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)].

As noted above, your production of drug products containing domperidone violates the FDCA. FDA is concerned with the public health risks associated with the compounding of domperidone for human use. After a 2005 FDA inspection revealed that your firm was producing domperidone drug products, FDA notified your firm that it should stop such production immediately. However, the March 2013 inspection of your facility found that your firm continued to produce drug products containing domperidone.

Misbranded Drug Products

Because the domperidone drug products and 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 CFR § 201.115].

In addition, your firm dispensed a budesonide product that is misbranded under section 502(a) of the FDCA. Under section 502(a) of the FDCA, a drug product is misbranded if its labeling is false or misleading in any particular. Your budesonide product is labeled with two conflicting routes of administration "For Inhalation Only/Twist top to open, pour into nebulizer reservoir" as well as "Irrigate 25mL into each nostril…" Therefore, the labeling for your budesonide product is misleading.

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 of the components used to make the drug and results in the drug being misbranded.

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 insanitary conditions included plant clothing, which aseptic technicians wear under reusable sterile gowns, which were stored on an open shelf a few feet from the toilet in your restroom. We also observed your personnel placing materials in the ISO 5 hood without disinfecting them, moving directly over open vials and syringes, stoppering by hand instead of using sterile tools or equipment, and using non-sterile wipes and non-sterile blue mats in the ISO 5 hood.

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 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 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 and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of such stability testing to determine appropriate storage conditions and expiration dates [21 CFR 211.166(a)].
3. Your firm does not have, for each batch of drug product purporting to be sterile and/or pyrogen-free, an appropriate laboratory determination of satisfactory conformance to final specifications for the drug product [21 CFR 211.167(a)].
4. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas [21 CFR 211.42(c)(10)(iv)].
5. Your firm failed to ensure that personnel involved in the manufacture, processing, packing, or holding of drug products wear clothing appropriate to protect drug products from contamination [21 CFR 211.28(a)].
6. Your firm does not have, for each batch of drug product, an appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release [21 CFR 211.165(a)].

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 of the components used to make the drug and results in the drug being adulterated.

D. Corrective Actions

In your response to the Form FDA 483 dated April 10, 2013, your firm indicates that you meet or exceed the current standards as outlined in United States Pharmacopeia (USP)-National Formulary (NF) General Chapter <797> Pharmaceutical Compounding-- Sterile Preparations. However, as discussed above, your firm has manufactured and distributed both drug products containing domperidone (which, as noted above, were not eligible for the exemptions provided by section 503A(a)) and also 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. Your firm's planned corrections do not meet the minimum requirements of 21 CFR part 211, and there is no assurance that such human drug products produced by your firm conform to the basic quality standards that ensure safety, identity, strength, quality, and purity.

During a telephone conversation on May 2, 2013, you indicated to FDA that your firm would cease sterile production and that you would hire "an expert to help" with your "GMPs." In your letter dated May 3, 2013, you state that your firm decided to immediately cease sterile production until "the FDA returns to the pharmacy advising that proposed sterile operations meet regulatory standards."

We acknowledge your letter dated August 27, 2013, in which you state that your firm would permanently discontinue the compounding of pre-mixed irrigation and nebulization drug products intended for nasal use,

which include budesonide products.

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. 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 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 contract testing laboratories to perform some of the required testing of your finished drug products. FDA inspected these laboratories in 2012 and 2013 and observed deficiencies in their practices. 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 C.F.R. 210.1(b), 21 C.F.R. 200.10(b).]

In addition, you should also correct the violations of sections 501(a)(2)(A) and 502(f)(1) of the FDCA, 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 and 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 violations, or you may inform us that you do not intend to resume production of sterile drugs. 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. In addition to taking appropriate corrective actions, you should notify this office prior to resuming production of any sterile drugs in the future. Your written 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,
/S/
Elizabeth W. Ormond
Acting Director, Florida District

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[1] *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).
[2] The CPG set forth a non-exhaustive list of factors that FDA considered in determining whether to take enforcement action when the scope and nature of a pharmacy's activities raised concerns. This CPG has been withdrawn in light of new legislation. See below.
[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] Drug Quality and Security Act, Public Law 113-54, 127 Stat. 587 (Nov. 27, 2013).
[5]The CQA contains a number of other provisions, including new exemptions and requirements for compounders seeking to operate as outsourcing facilities. A discussion of the CQA and the agency's plans to implement the new law may be found at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm .
[6] 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.

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