Inspections, Compliance, Enforcement, and Criminal Investigations

Nature's Pharmacy & Compounding Center 5/9/14

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Atlanta District
60 8th Street, N.E.
Atlanta, GA 30309

May 9, 2014

VIA UPS

WARNING LETTER
(14-ATL-07)

William B. Cheek, Pharmacist and Co-owner
Nature's Pharmacy & Compounding Center
752 Biltmore Ave
Asheville, NC 28803-2558

Dear Mr. Cheek:

From November 12, 2013 to November 22, 2013, a U.S. Food and Drug Administration (FDA) investigator conducted an inspection of your facility, Nature's Pharmacy & Compounding Center, 752 Biltmore Ave, Asheville, NC 28803-2558. During the inspection, the investigator noted that you were not receiving valid prescriptions for individually-identified patients for a portion of the drug products you were producing. In addition, the investigator observed serious deficiencies in your practices for producing drug products intended or expected to be sterile, which put patients at risk. For example, your compounding procedure for Lidocaine 4% solution/personal lubricant (1:1) Gel used for urethral injection is to mix sterile lidocaine with non-sterile lubricant in a non-sterile **(b)(4)** without any further sterilization before it is filled into sterile bags and sealed. In addition, your firm failed to demonstrate through appropriate studies that your **(b)(4)** is able to provide adequate protection of the area in which products intended or expected to be sterile are processed. Therefore, your products may be produced in an environment that poses a significant contamination risk. In addition, you do not use sterile disinfectants, including a sporicidal agent, for disinfection of the area. FDA issued a Form FDA 483 to your firm on November 22, 2013. Furthermore, a lack of sterility assurance resulted in a voluntary recall of product on November 13, 2013.

Based on this inspection, it appears that you have produced 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 (CPG) (2002), which was then in effect [2] During the FDA inspection, the investigator 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]

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, 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. [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 drug products that you manufacture and distribute without valid prescriptions for individually-identified patients are misbranded drugs in violation of section 502(f)(1) [21 U.S.C. § 352(f)(1)] of the FDCA. In addition, your drug products intended or expected to be sterile 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 drug products intended or expected to be sterile that 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, 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. An FDA investigator 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)].

Misbranded Drug Products

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 drug 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). It is also 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, an FDA investigator noted that drug products 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 [21 U.S.C. § 351(a)(2)(A)]. Examples of these conditions include that your compounding procedure for Lidocaine 4% solution/personal lubricant (1:1) Gel used for urethral injection is to mix sterile lidocaine with non-sterile lubricant in a non-sterile **(b)(4)** without any further sterilization process before it is filled into sterile bags and sealed. In addition, your firm failed to demonstrate through appropriate studies that your **(b)(4)** is able to provide adequate protection of the area in which products intended or expected to be sterile are processed. Therefore, your products may be produced in an environment that poses a significant contamination risk. Furthermore, you do not use sterile disinfectants, including a sporicidal agent, for disinfection of the area.

An FDA investigator 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 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 failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

4. Your firm did 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)).

5. 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)).

6. Your firm failed to establish an adequate air supply filtered through high-efficiency particulate air filters under positive pressure in the aseptic processing areas (21 CFR 211.42(c)(10)(iii)).

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

C. Corrective Actions

We acknowledge your action on November 13, 2013, to voluntarily recall all sterile products within expiry, as well as your written response to the Form FDA 483 on November 26, 2013, notifying FDA that you have permanently ceased all sterile compounding operations.

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 and design. A third party consultant with relevant sterile drug manufacturing expertise could be useful in conducting this comprehensive evaluation.

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 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.

You should also correct the violations of FDCA sections 501(a)(2)(A) and 502(f)(1) noted above.

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 and FDA regulations.

If you decide to resume sterile operations, 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 may re-inspect to verify corrective actions have been completed.

Within fifteen working days of receipt of this letter, please notify this office in writing if you have taken any specific steps to correct violations, or you may inform us that you do not intend to resume production of sterile drugs. If you intend to resume production of sterile drugs in the future, 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:

Marie Mathews, Compliance Officer
FDA Atlanta District Office
U.S. Food and Drug Administration
60 8th Street, N.E.
Atlanta, GA 30309

If you have questions regarding any issues in this letter, please contact our office at 404-253-1161.

Sincerely,
/S/
Ingrid A. Zambrana
District Director

cc: Michael Rodgers, Pharmacist and Co-owner
Nature's Pharmacy & Compounding Center
752 Biltmore Ave
Asheville, NC 28803-2558

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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[1].
[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.

Links on this page:

1. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm