Inspections, Compliance, Enforcement, and Criminal Investigations

Blue Ridge Pharmacy and Compounding Center 4/30/14

Department of Health and Human Services

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

April 30, 2014

VIA UPS

WARNING LETTER
(14-ATL-06)

Wendy L. Haun, R.Ph., Owner
Blue Ridge Pharmacy and Compounding Center
2601 Blue Ridge Rd
Raleigh, NC 27607

Dear Ms. Haun:

From October 15, 2013, to October 23, 2013, a U.S. Food and Drug Administration (FDA) investigator conducted an inspection of your facility, Blue Ridge Pharmacy and Compounding Center, located at 2601 Blue Ridge Rd., Raleigh, NC 27607. 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 sterile drug products, which could lead to contamination of the products, potentially putting patients at risk. For example, you do not use sterile disinfectants, including a sporicidal agent, for disinfection of the glove box, an area where you perform aseptic operations. The glove box gloves used to perform aseptic operations are not sterile and are changed every **(b)(4)** without a maintenance procedure that requires identification and replacement of those with pin holes prior to the replacement time. Additionally, the glove box is located in an unclassified carpeted room without HEPA filtered air and this room does not have covered walls or caulked ceilings that are easily cleanable. FDA issued a Form FDA 483 to your firm on October 23, 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 sections 502(f)(1) [21 U.S.C. § 352(f)(1)] of the FDCA. 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 drug 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, the manufacture of those 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. 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 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 you do not use sterile disinfectants, including a sporicidal agent, for the disinfection of the glove box, an area where you perform aseptic operations. Instruments, materials, and supplies used in aseptic processing are not disinfected prior to entering the glove box and there is no environmental monitoring. The glove box gloves used to perform aseptic operations are not sterile and are changed every **(b)(4)** without a maintenance procedure that identifies and replaces those with pin holes prior to the replacement time. Additionally, the glove box is located in an unclassified carpeted room without HEPA filtered air and this room does not have covered walls or caulked ceilings that are easily cleanable.

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

2. 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)).

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 failed to establish an adequate system for maintaining equipment used to control the aseptic conditions (21 CFR 211.42(c)(10)(vi)).

5. 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)).

6. 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)).

7. 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)).

8. 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 October 18, 2013, to recall all sterile products within expiry and your written statement on October 30, 2013, notifying FDA that you have permanently ceased all sterile compounding operations as of August 20, 2013.

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 such drug product(s) produced by your firm conform to the basic quality standards that ensure 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* 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. FDA inspected this laboratory **(b)(4)** and observed deficiencies in its 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 drugs you introduce into interstate commerce are neither adulterated nor misbranded. *See* 21 CFR 210.1(b), 21 CFR 200.10(b).

If you resume sterile compounding, 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

---

[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