Inspections, Compliance, Enforcement, and Criminal Investigations

PharMEDium Services, LLC 7/18/14

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Chicago District
550 West Jackson Blvd. 15th Floor
Chicago, Illinois 60661
Telephone: 312-353-5863

July 18, 2014

WARNING LETTER
CHI-10-14

VIA UPS NEXT DAY

Mr. William R. Spalding
Chief Executive Officer
PharMEDium Services, LLC
Two Conway Park
150 North Field Drive
Suite 350
Lake Forest, IL 60045

Dear Mr. Spalding:

Between February 19, 2013 and March 22, 2013, U.S. Food and Drug Administration (FDA) investigators conducted inspections of your facilities, PharMEDium Services, LLC, located at 913 N. Davis Ave., Cleveland, MS, 38732; 43 Distribution Blvd., Edison, NJ, 08817; 6100 Global Dr., Memphis, TN, 38141; and 12620 W. Airport Blvd. Ste. 130, Sugar Land, TX, 77478. The investigators observed serious deficiencies in your practices for producing sterile drug products at each of your facilities, which put patients at risk. For example, at some of your facilities, our investigators observed that operators did not properly sanitize their hands after touching non-sterile equipment and processed sterile drug products with exposed skin on their faces and wearing non-sterile masks. In addition, our investigators found 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 Form FDA 483s at your facilities between February 22, 2013 and March 22, 2013.

Based on these inspections, it appears that you are producing drugs that violate the Federal Food, Drug, and Cosmetic Act (FDCA).

FDA acknowledges that PharMEDium registered all of its facilities with FDA as 503B outsourcing facilities on December 11, 2013.

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 inspections, the investigators observed that your firm does not receive valid prescriptions for individually-identified patients for 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.

The CQA adds a new section 503B to the FDCA [21 U.S.C. § 353b].[5] Under section 503B(b), a compounder can register as an outsourcing facility with FDA.[6] As noted previously, PharMEDium registered all of the facilities referenced in this letter with FDA as section 503B outsourcing facilities on December 11, 2013. Drug products compounded in a registered outsourcing facility can qualify for exemptions from the FDA approval requirements in section 505 of the FDCA [21 U.S.C. § 355(a)] and the requirement to label products with adequate directions for use under section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)] if the requirements in section 503B are met. In addition, prescriptions for individually-identified patients are not required for products produced under section 503B of the FDCA.

To qualify for the exemptions under section 503B, the drug products must be compounded in a 503B outsourcing facility that meets all of the conditions set forth in section 503B of the FDCA, which include, but are not limited to, submitting adverse event reports, labeling compounded products with certain information, and compounding drug products by or under the direct supervision of a licensed pharmacist. In addition, outsourcing facilities must comply with other provisions of the FDCA, including the current good manufacturing practice (CGMP) requirements under section 501(a)(2)(B) [21 U.S.C. § 351(a)(2)(B)] and the prohibition on preparing, packing, or holding drugs under insanitary conditions found in section 501(a)(2)(A) [21 U.S.C. § 351(a)(2)(A)].

Generally, CGMP requirements for finished drug products are established in Title 21 of the Code of Federal Regulations (CFR) parts 210 and 211. As discussed further below, PharMEDium does not comply with certain CGMP requirements. It is also noteworthy that this is not the first Warning Letter that FDA has issued to PharMEDium for CGMP violations. FDA issued a Warning Letter on April 13, 2007 noting CGMP violations at two of your facilities.

B. Violations of FDCA

Because the drug products that you manufactured and distributed without valid prescriptions for individually-identified patients were not the subject of approved applications, they are unapproved new drugs in violation of section 505(a) of the FDCA. In addition, because these products were intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners, adequate directions could not be written for them so that a layman could 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. In addition, your sterile drug products are prepared, packed, or held under insanitary conditions whereby they may have been contaminated with filth or rendered injurious to health. As such, all sterile drug products you manufacture are adulterated within the meaning of section 501(a)(2)(A) of the FDCA. Furthermore, because you manufactured and distributed your drugs without valid prescriptions for individually-identified patients, the manufacture of those drugs was also

subject to FDA's CGMP regulations for Finished Pharmaceuticals, Title 21 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.

Because your facilities are now registered as section 503B outsourcing facilities, this letter focuses on the insanitary conditions and violations of CGMP requirements that continue to apply even though you registered your facilities as outsourcing facilities.

Insanitary Conditions Observed During FDA's Inspections

Based on the February and March 2013 inspections of your facilities, FDA investigators noted that your sterile drug products were prepared, packed, or held under insanitary conditions whereby they may have been contaminated with filth, or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) [21 U.S.C. §351 (a)(2)(A)] of the FDCA. For example, at some of your facilities our investigators observed that:

1. Your firm's operators did not properly sanitize their hands after touching non-sterile equipment and were observed processing sterile drug products with exposed skin on their faces and while wearing non-sterile masks. Furthermore, we observed operators at one facility re-using gowns throughout the day and during periods of production.

2. Your firm did not perform personnel monitoring of all operators at least daily during periods of production to examine the practices of personnel and assess contamination risk to product by poor practices.

3. Your firm did not demonstrate through appropriate studies that your hoods are able to provide adequate protection of the ISO 5 area in which sterile products are processed. For example, your airflow studies do not consider the full operational conditions of the room, including the fact that your firm has numerous hoods within the clean room and that a single hood is used to support multiple compounding processes that are occurring at the same time.

As noted above, outsourcing facilities, like any other compounder, may not prepare, pack, or hold drugs under insanitary conditions (section 501(a)(2)(A) of the FDCA).

CGMP Violations Observed During FDA's Inspections

FDA investigators also noted CGMP violations at your facilities, causing the drug products for which you did not obtain valid prescriptions for individually-identified patients to be adulterated under section 501(a)(2)(B) of the FDCA . Such violations observed at some of your facilities include, for example:

1. Your firm failed to adequately design the facility with adequate separation or defined areas or such other control systems necessary to prevent contamination or mix-ups (21 CFR 211.42(b)).

2. Your firm failed to perform operations within specifically defined areas of adequate size and to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups during the course of certain procedures (21 CFR 211.42(c)).

3. 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 processes (21 CFR 211.113(b)).

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

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

7. 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)).

8. 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)).

9. Your firm did not have, for each batch of drug product, 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)).

As noted above, outsourcing facilities must comply with current good manufacturing practice (CGMP) requirements under section 501(a)(2)(B) of the FDCA. On July 1, 2014, FDA issued a draft guidance, *Current Good Manufacturing Practice — InterimGuidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act.* Until final regulations are promulgated, this draft interim guidance describes FDA's expectations regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211. You should consult the interim guidance for FDA's expectations regarding the particular provisions in 21 CFR Parts 210 and 211 cited above pending the development of the new regulations. Your attention is directed in particular to the provisions with regard to sterility testing and stability testing, and the establishment of beyond use dates.

Corrective Actions

In your responses submitted March 18, 2013, March 20, 2013, March 21, 2013, and April 12, 2013, you described certain corrective actions you took in response to the Form FDA 483 observations. You also indicated that you adhere to USP Chapter <797> "Pharmaceutical Compounding – Sterile Preparations" and comply with statutory GMPs. You also acknowledged that companies like yours need to more closely align with the CGMP requirements in 21 CFR 211. Since providing these responses, you registered your four facilities as outsourcing facilities, and are subject to CGMP requirements under the new law. In addition, you remain subject to section 501(a)(2)(A)) of the FDCA.

Although several of your proposed corrective actions appear adequate, others are deficient. In your response to our observation of inadequate media fills, you indicated that you have made procedural changes to include an additional step that represents the continuous processes of pooling, subassembly, and finished container filling as well as packaging. You also stated that you performed a growth promotion study. These corrections will improve your knowledge of your process, but will not provide sufficient information to assess the risk in the clean room to product sterility assurance since your procedures still require media fills to be performed in an area physically segregated from production.

In your response to our observation of inadequate air flow studies, you indicated that you will require documentation of various items such as the equipment, the equipment placement, presence of separator panels that allow for two operations to occur within the same hood, and location of personnel that are present during dynamic air flow studies. Because you have sterile compounding activities occurring simultaneously in up to **(b)(4)** hoods in some of your firm's clean rooms, and at times use a single hood to support multiple compounding processes at the same time, your air flow studies should also account for these activities.

In your response to our observation of inadequate gowning of operators during production, you indicated that sterile gowning is not a USP <797> requirement, but that you procedurally require operators to wear sterile gowns. Your response is inadequate because your procedure continues to allow operators to have exposed skin and use non-sterile facemasks, and you did

not address training that may be required to ensure employees are properly gowned. Furthermore, the procedure still allows for gowning to be reused throughout the day which poses an unacceptable risk of contamination to products.

In your response to our observation of poor aseptic practices, you committed to making procedural changes to prohibit operators from leaning into hoods and enhanced the procedure for component transfers into the hood. This is inadequate to address the fundamental lack of proper aseptic behaviors that was observed and the disregard for written procedures.

Your firm's planned corrections do not meet the minimum requirements of 21 CFR parts 210 and 211, and there is no assurance that the drug products produced by your firm conform to the basic quality standards that ensure safety, identity, strength, quality, and purity.

FDA strongly recommends that your management immediately undertake a comprehensive assessment of your operations corporate-wide, 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.

Conclusion

The violations cited in this letter are not intended to be an all-inclusive statement of violations at your facilities. 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.

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 you have taken to correct 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, include your reasoning and any supporting information for our consideration. If the corrective actions cannot be completed within fifteen working days, state the reason for the delay and the time frame within which the corrections will be completed. Your written notification should be addressed to:

Carrie Ann Plucinski, Compliance Officer
Food and Drug Administration
550 W. Jackson Blvd. Suite 1500
Chicago, IL 60661

If you have questions regarding any issues in this letter, please contact Ms. Plucinski at 312-596-4224 or via email at carrie.plucinski@fda.hhs.gov.

Sincerely,
/S/
Scott J. MacIntire
District Director

cc: Dr. Yashwant Amin
Director of Drug Compliance
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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] *See* Pub. L. No. 113-54, § 102(a), 127 Stat. 587, 587-588 (2013).
[6] *See* Draft Guidance for Industry, "Registration for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act," (December, 2013).

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