Brown's Compounding Center, Inc. 8/17/16

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Denver District Office
Building 20-Denver Federal Center
P.O. Box 25087
Denver, Colorado 80225-0087
TELEPHONE: 303-236-3000

August 17, 2016

UPS OVERNIGHT
RETURN RECEIPT REQUESTED

WARNING LETTER

Darby C. Brown, President and CEO
Brown's Compounding Center, Inc.
11753 Dunrich Road
Parker, CO 80138

Ref.#: DEN-16-15-WL

Dear Mr. Brown:

From July 28, 2014 to August 11, 2014, U.S. Food and Drug Administration (FDA) investigators conducted an inspection of your facility, Brown's Compounding Center, Inc., located at 13796 Compark Blvd. #100, Englewood, CO 80112. During the 2014 inspection of your facility, the investigators 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 investigators observed serious deficiencies in your practices for producing sterile drug products, which put patients at risk. For example, investigators noted that your firm failed to demonstrate through appropriate studies that your hoods were able to provide adequate protection of the ISO 5 areas in which

sterile products were processed. Therefore, your products may have been produced in an environment that posed a significant contamination risk. FDA issued a Form FDA 483 to your facility on August 11, 2014. FDA acknowledges receipt of your facility's response, dated August 13, 2014.

You registered with FDA as an outsourcing facility under section 503B of the Federal Food, Drug, and Cosmetic Act (FDCA) [21 U.S.C. § 353b] **[1]** on December 22, 2014. From April 20, 2015, to April 27, 2015, while your facility was registered as an outsourcing facility, FDA investigators again inspected your facility. During the 2015 inspection, the investigators again observed serious deficiencies in your practices for producing sterile drug products, which put patients at risk. For example, the investigators observed operators resting their gloved hands on the surfaces of the laminar airflow workbenches as well as operators not sanitizing their gloved hands after touching equipment outside of the aseptic production area. Moreover, your firm again 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 have been produced in an environment that posed a significant contamination risk. In addition, the investigators observed that you failed to meet the conditions under section 503B of the FDCA necessary for drugs produced by an outsourcing facility to qualify for exemptions from certain requirements under the FDCA. FDA issued a Form FDA 483 to your facility on April 27, 2015. FDA acknowledges receipt of your facility's response, dated April 28, 2015.

You deregistered as an outsourcing facility on July 7, 2015. Based on information known to FDA, your firm ceased all compounding operations as of June 10, 2015, surrendered its pharmacy license with the State of Colorado on June 22, 2015, and is no longer operational.

Although as of the date of this letter your facility is no longer registered as an outsourcing facility and is not operational, this letter discusses violations identified during the two inspections referenced above.

Based on these inspections, it appears your facility produced drugs that violate the FDCA.

A. Compounded Drugs under the FDCA

Section 503A of the FDCA [21 U.S.C. § 353a] describes the conditions under which certain compounded human drug products qualify for exemptions from three sections of the FDCA: compliance with Current Good Manufacturing Practice (CGMP) requirements, section 501(a)(2)(B) of the FDCA [21 U.S.C. § 351(a)(2)(B)]; labeling with adequate directions for use, section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)]; and FDA approval prior to marketing, section 505 of the FDCA [21 U.S.C. § 355]. Receipt of valid prescriptions for individually-identified patients is one of the conditions that must be met for drug products to qualify for the exemptions under section 503A of the FDCA. During the 2014 inspection, which was conducted before you registered as an outsourcing facility under section 503B, the investigators observed that your firm did not receive valid prescriptions for individually-identified patients for a portion of the drug products you produced.

Another condition that must be met for drug products to qualify for the exemptions under section 503A of the FDCA is that the compounded drug products do not appear on a list published by the FDA at Title 21 Code of Federal Regulations (CFR) Part 216 of drugs that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective ("withdrawn or removed list"). During the 2014 inspection, investigators observed that your firm compounded two drug products that appear on the withdrawn or removed list at 21 CFR Part 216. Specifically, you compounded:

- Chlorhexidine Gluconate Gel 1% for application around a dental implant. The withdrawn or removed list includes "all tinctures of chlorhexidine gluconate formulated for use as a patient preoperative skin preparation."
- Tetracycline 50mg/ml for a 10 year-old patient. The withdrawn or removed list includes "all liquid oral drug products formulated for pediatric use containing tetracycline in a concentration greater than 25 milligrams/milliliter."

Accordingly, the drugs you compounded, at the time of FDA's 2014 inspection were not entitled to the exemptions in section 503A of the FDCA.

The Drug Quality and Security Act (DQSA) was enacted on November 27, 2013. Title I of the DQSA, the Compounding Quality Act (CQA), added a new section 503B to the FDCA. Under section 503B(b), a compounder can register as an outsourcing facility with FDA. Drug products compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility can qualify for exemptions from the drug approval requirements in section 505 of the FDCA, the requirement in section 502(f)(1) of the FDCA that labeling bear adequate directions for use, and the Drug Supply Chain Security Act requirements in section 582 of the FDCA [21 U.S.C. § 360eee-1] if the conditions in section 503B of the FDCA are met. As noted, you registered with FDA as an outsourcing facility under section 503B on December 22, 2014, and were registered as an outsourcing facility at the time of the 2015 inspection, prior to your deregistration on July 7, 2015.

An outsourcing facility, which is defined in section 503B(d)(4) of the FDCA [21 U.S.C. § 353b(d)(4)], is a facility at one geographic location or address that — (i) is engaged in the compounding of sterile drugs; (ii) has elected to register as an outsourcing facility; and (iii) complies with all of the requirements of this section. Outsourcing facilities must comply with other provisions of the FDCA, including section 501(a)(2)(B) [21 U.S.C. § 351(a)(2)(B)], regarding current good manufacturing practice (CGMP), and section 501(a)(2)(A) [21 U.S.C. § 351(a)(2)(A)], regarding insanitary conditions. Generally, CGMP requirements for the preparation of drug products are established in Title 21 of the Code of Federal Regulations (CFR) parts 210 and 211.

B. Violations of the FDCA

During both the 2014 and the 2015 inspections, the investigators noted that drug products that were intended or expected to be sterile were prepared, packed, or held under insanitary conditions whereby they may have been contaminated with filth or rendered injurious to health, causing them to be adulterated within the meaning of section 501(a)(2)(A) of the FDCA. Furthermore, because you compounded and distributed drug products without valid prescriptions for individually-identified patients and drug products that appear on the withdrawn or removed list at 21 CFR Part 216, prior to registering as an outsourcing facility, none of the drug products you

compounded qualified for the exemptions under section 503A of the FDCA and were therefore subject to FDA's CGMP requirements for the preparation of drug products codified in Title 21 of the Code of Federal Regulations (CFR) Parts 210 and 211 (CGMP requirements). In addition, all drugs compounded by an outsourcing facility, are subject to FDA's CGMP requirements. During both the 2014 and 2015 inspections, FDA investigators observed significant CGMP violations at your facility, causing all drug products you compounded to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA.

In addition, during the 2015 inspection, which was conducted while you were registered as an outsourcing facility under section 503B of the FDCA, the FDA investigators observed that your facility failed to meet the conditions of section 503B. For example, during the 2015 inspection, FDA investigators noted:

1. None of your facility's drug products included the following statements on the label: the statement, "This is a compounded drug", and the date the drug was compounded (Section 503B(a)(10)(A) of the FDCA [21 U.S.C. §353b(a)(10)(A)]). In addition, some of your facility's drug products did not include information on the container to facilitate adverse event reporting (Section 503B(a)(10)(B) of the FDCA [21 U.S.C. §353b(a)(10)(B)]).

2. Your facility failed to submit a complete report to FDA upon initial registration as an outsourcing facility in December 2014 identifying the drug products (sterile and non-sterile) that you compounded during the previous 6-month period (section 503B(b)(2) of the FDCA [21 U.S.C. §353b(b)(2)]).

Because the drug products that you manufactured and distributed both prior to registration as an outsourcing facility and after you registered as an outsourcing facility did not qualify for the exemptions of sections 503A and 503B[2] of the FDCA respectively, and were not the subject of approved applications, they were unapproved new drugs and misbranded drugs in violation of sections 505(a) and 502(f)(1) of the FDCA.

Specific violations are described below.

Adulterated Drug Products

FDA investigators noted that drug products compounded in your facility that were 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. For example, during the 2015 inspection, the investigators observed operators resting their gloved hands on the surfaces of the laminar airflow workbenches as well as operators not sanitizing their gloved hands after touching equipment outside of the aseptic production area. In addition, during both the 2014 and 2015 inspections, 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 have been produced in an environment that posed a significant contamination risk.

During both the 2014 and 2015 inspections, FDA investigators noted CGMP violations at your facility, causing your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. 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)).

Outsourcing facilities must comply with CGMP requirements under section 501(a)(2)(B) of the FDCA. FDA's regulations regarding CGMP requirements for the preparation of drug products have been established in 21 CFR Parts 210 and 211. Furthermore, as previously stated, the drugs you compounded before registering as an outsourcing facility, were also subject to 21 CFR Parts 210 and 211.

Under section 301(a) of the FDCA [21 U.S.C. § 331(a)], the introduction or delivery for introduction into interstate commerce of any drug that is adulterated is a prohibited act. Further, 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 and results in the drug being adulterated.

Unapproved New Drug Products

You did not have any FDA-approved applications on file for the drug products for which you did not obtain valid prescriptions for individually-identified patients, or the drugs you compounded that appear on the withdrawn or removed list at 21 CFR Part 216 prior to registering as an outsourcing facility, or for the drug products you compounded while registered as an outsourcing facility.[3] 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 or delivered for introduction into interstate commerce unless an application approved by FDA under section 505 of the FDCA is in effect for the drug.

Misbranded Drug Products

As stated above the drug products that you compounded prior to registering as an outsourcing facility and while you were an outsourcing facility did not qualify for the exemptions under sections 503A and 503B of the FDCA respectively, including the exemption from the requirements of section 502(f)(1) concerning adequate directions for use. All of these drug products were intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners; therefore, adequate directions for use cannot be written for them so that a layman can use these products safely for their intended uses. Consequently, their labeling failed to bear adequate directions for their intended uses, causing them to be misbranded under section 502(f)(1) of the FDCA (*see, e.g.,* 21 CFR 201.115). The

introduction or delivery for introduction into interstate commerce of these products therefore violates section 301(a) of the FDCA. Further, it is a prohibited act under section 301(k) of the FDCA 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 and results in the drug being misbranded.

Failure to Report Drugs

As noted above, your facility failed to submit a complete report to FDA upon initial registration as an outsourcing facility in December 2014 identifying all the drug products (sterile and non-sterile) that you compounded during the previous 6-month period (section 503B(b)(2) of the FDCA [21 U.S.C. §353b(b)(2)]). The failure to report drugs by an entity that is registered with FDA in accordance with section 503B(b) is a prohibited act under section 301(ccc)(3) of the FDCA [21 U.S.C. § 331(ccc)(3)].

C. Corrective Actions

In your letters dated August 13, 2014, and April 28, 2015, responding to the Form FDA 483s issued to your firm on August 11, 2014, and April 27, 2015, respectively, you committed to take numerous corrective actions and described certain corrective actions you had taken in response to the Form FDA 483 observations.

We acknowledge that your firm ceased all compounding operations as of June 10, 2015, and is no longer operational.

If you decide to resume operations in the future, before resuming production of sterile drugs, FDA strongly recommends that your management 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.

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, including FDA regulations.

If you decide to resume operations at this facility, 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, or you may confirm that you do not intend to resume production of sterile drugs at this facility. If you intend to resume production of sterile drugs at this facility, please provide an explanation of each step being taken to prevent the recurrence of violations, as well as copies of

related documentation prior to resuming such operations. 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. Your written notification should refer to the Warning Letter Number DEN-16-15-WL. Please address your reply to Matthew R. Dionne, Pharm.D., Compliance Officer, at the address above.

If you have questions regarding the contents of this letter, please contact Dr. Dionne via email at Matthew.Dionne@fda.hhs.gov or by phone at 303-236-3064.

Sincerely,
/S/
LaTonya M. Mitchell
District Director
Denver District

CC:
Robert C. Blume, Partner
Gibson & Dunn
1801 California Street
Denver, CO 80202.

---

[1] *See* Pub. L. No. 113-54, § 102(a), 127 Stat. 587, 587-588 (2013).

[2] See, e.g., section 503B(a)(11) of the FDCA [21 U.S.C. § 353b(a)(11)].

[3] The specific products made by your firm were drugs within the meaning of section 201(g) of the Act, [21 U.S.C. § 321(g)] because they were intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases and/or because they were intended to affect the structure or any function of the body. Further, they were “new drugs” within the meaning of section 201(p) of the FDCA [21 U.S.C. § 321(p)] because they were not generally recognized as safe and effective for their labeled uses.