U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Delta Pharma, Inc. 12/9/14

Department of Health and Human Services

Public Health Service
Food and Drug Administration
New Orleans District
404 BNA Drive
Building 200 – Suite 500
Nashville, TN 37217
Telephone: (615) 366-7801
FAX: (615) 366-7802

December 9, 2014

WARNING LETTER NO. 2015-NOL-04

UNITED PARCEL SERVICE
DELIVERY SIGNATURE REQUESTED

Tommy T. Simpson, President
Delta Pharma, Inc.
114 W. Mulberry Street
Ripley, Mississippi 38663-1709

Dear Mr. Simpson:

From September 24-27 and October 2, 2013, U.S. Food and Drug Administration (FDA) investigators conducted an inspection of your facility, Delta Pharma, Inc. (Delta), located at 114 W. Mulberry Street, Ripley, Mississippi. FDA inspected your firm after receiving reports of adverse events in four patients who received intra-articular injections of Deltalone-40 (triamcinolone and lidocaine) produced by your firm. The investigators observed serious deficiencies in your practices for producing sterile drug products at your facility, which put patients at risk. For example, our investigators observed, and verified during discussions with management, the disinfectants used in the clean room are not sterile, and that equipment and materials are not disinfected before introduction into the ISO 5 area. In addition, our investigators found the design and operation of the clean room is not adequate to prevent the influx of lower quality air into the clean room and the ISO 5 area from the unqualified and un-classified gowning room. Specifically, the room certification report you provided indicated the room differential pressure was significantly below the levels required to ensure the air quality would be maintained during

production. Furthermore, your firm failed to demonstrate through appropriate studies that your hood is able to provide adequate protection of the ISO 5 area in which sterile products are processed. Therefore, your products may be produced in an environment that poses a significant contamination risk. FDA issued a Form FDA 483, Inspectional Observations (Form FDA 483), to your firm on October 2, 2013. We acknowledge your responses dated November 8 and December 18, 2013, and August 1, 2014, to the Form FDA 483.

Based on the inspection, it appears you are producing drugs which violate the Federal Food, Drug, and Cosmetic (the Act).

FDA also acknowledges Delta registered its facility with FDA as a 503B outsourcing facility on August 6, 2014.

A. Compounded Drugs Under the Act

At the time FDA inspected your facility, there were conflicting judicial decisions regarding the applicability of Section 503A of the Act [21 *United States Code* (USC) 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 Act and the agency's Compliance Policy Guide 460.200 (CPG) (2002), which was then in effect.[2] During the FDA inspection, the investigators observed your firm does not receive valid prescriptions for individually-identified patients for the drug products you produce. Based on this alone, those drugs were not entitled to the statutory exemptions for compounded drugs described in Section 503A of the Act 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 Section 503A of the Act by eliminating the advertising restrictions that had been the basis for conflicting judicial decisions. The CQA otherwise left Section 503A intact, and so clarified the remainder of Section 503A, including the requirement of valid prescriptions for individually-identified patients, is applicable in every federal judicial circuit.

As you are aware, the CQA adds a new Section 503B of the Act [21 USC 353b].[5] Under Section 503B(b), a compounder can register as an outsourcing facility with FDA.[6] As noted previously, Delta registered with FDA as a Section 503B outsourcing facility on August 6, 2014. Drug products compounded in a registered outsourcing facility can qualify for exemptions from the FDA approval requirements in Section 505 of the Act [21 USC 355(a)], the requirement to label products with adequate directions for use under Section 502(f)(1) of the Act [21 USC 352(f)(1)] and track and trace requirements of Section 582 of the Act [21 USC 360eee-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 Act.

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 Act, 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 Act, including the Current

Good Manufacturing Practice (CGMP) requirements under Section 501(a)(2)(B) [21 USC 351(a)(2)(B)] and the prohibition on preparing, packing, or holding drugs under insanitary conditions found in Section 501(a)(2)(A) [21 USC 351(a)(2)(A)].

Generally, CGMP requirements for finished drug products are established in Title 21, *Code of Federal Regulations* (CFR) Parts 210 and 211. As discussed further below, Delta does not comply with certain CGMP requirements. It is also noteworthy this is not the first warning letter FDA has issued to Delta for CGMP violations. FDA issued a warning letter on September 17, 2004, noting CGMP violations at your facility.

B. Violations of the Act

Because the drug products 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 Act. 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 Act. In addition, FDA investigators noted that drug products compounded in your facility which 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. As such, all sterile drug products you compound are adulterated within the meaning of Section 501(a)(2)(A) of the Act. Furthermore, because Delta is an outsourcing facility, the drug products compounded at that facility are subject to CGMP requirements. As more specifically described below, 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 Act.

Because your facility is now registered as a Section 503B outsourcing facility, this letter focuses on the insanitary conditions and violations of CGMP requirements that continue to apply even though you registered as an outsourcing facility.

Insanitary Conditions Observed During FDA's Inspections

Based on the September 24 and October 2, 2013, inspection of your facility, FDA investigators noted that sterile drug products compounded in your facility 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) of the Act. For example, our investigators observed and verified during discussions with management, the disinfectants used in the clean room are not sterile, and equipment and materials are not disinfected before introduction into the ISO 5 area. In addition, our investigators found the design and operation of the clean room is not adequate to prevent influx of lower quality air into the clean room and the ISO 5 area from the unqualified and un-classified gowning room. Specifically, the room certification report you provided, indicated the room differential pressure was significantly below the levels required to ensure the air quality would be maintained during production. Furthermore, your firm failed to demonstrate through appropriate studies that your hood is able to provide adequate protection of the ISO 5 area in which sterile products are processed. Therefore, your products may be produced in an environment that poses a significant contamination risk.

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 Act].

CGMP Violations Observed during FDA's Inspections

FDA investigators also noted CGMP violations at your facility, 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 Act. Such violations observed at your facility 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 include validation of all aseptic and sterilization processes [21 CFR 211.113 (b)].

2. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas [21 CFR 211.42(c)(10)(iv)].

3. Aseptic processing areas are deficient regarding air supply that is filtered through high -efficiency particulate air filters under positive pressure regardless of whether flow is laminar or non-laminar [21 CFR 211.42(c)(10)(iii)].

4. 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)].

As noted above, outsourcing facilities must comply with CGMP requirements under Section 501(a)(2)(B) of the Act. On July 1, 2014, FDA issued a draft guidance, *Current Good Manufacturing Price — Interim Guidance 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 210 and 211.

You should consult the interim guidance for FDA's expectations regarding the particular provisions in 21 CFR 210 and 211 cited above pending the development of the new regulations.

Corrective Actions

In your responses submitted November 8, December 18, 2013, and August 1, 2014, you described certain corrective actions you took in response to Form FDA 483 observations. You also indicated you adhere to USP Chapter <797> "Pharmaceutical Compounding – Sterile Preparations" and comply with statutory GMPs. In a letter dated August 1, 2014, your attorney indicated that your management has determined you are already in compliance with the CGMP guidance on outsourcing facilities. On August 6, 2014, you registered as an outsourcing facility. As an outsourcing facility you are subject to CGMP requirements in addition to remaining subject to Section 501(a)(2)(A) of the Act.

We have reviewed your firm's planned corrections, as documented in your three responses, and have determined they do not meet the minimum requirements of 21 CFR 210 and 211, and there is no assurance the drug products produced by your firm conform to the basic quality standards that ensure safety, identity, strength, quality, and purity.

In your responses, you described certain corrective actions you took in response to the Form FDA 483 observations. Although several of your proposed corrective ions appear adequate, others are deficient. For example, there is no evidence the smoke studies provided were conducted under dynamic conditions. The media fill SOP is deficient (e.g., does not represent your actual manufacturing prices). The differential pressure between the clean room and the gowning room does not meet minimum specifications between cleanrooms and unclassified areas.

FDA strongly recommends 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.

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 assure 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 ion without further notice, including, without limitation, seizure and injunction.

Within 15 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 the products discussed above are in violation of the Act, include your reasoning and any supporting information for our consideration. If the corrective ions cannot be completed within 15 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:

Kari Batey, Compliance Officer
Food and Drug Administration
404 BNA Drive, Building 200, Suite 500
Nashville, TN 37217

If you have questions regarding any issues in this letter, please contact Ms. Batey at 615-366-7808 or via email at kari.batey@fda.hhs.gov.

Sincerely,
/S/
Ruth P. Dixon
District Director
New Orleans District

cc:

Jim M. Greenlee, Attorney
Holcomb Dunbar Attorneys
400 South Lamar, Suite A
Post Office Drawer 707
Oxford, Mississippi 38655-0707

Cheryl Atwood, Commissioned Official
Mississippi Board of Pharmacy
6360 I-55 North, Suite 400
Jackson, Mississippi 39211

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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 fors that FDA considered in determining whether to take enforcement ion when the scope and nature of a pharmacy's ivities raised concerns. This CPG has been withdrawn in light of new legislation. See below.
[3] *See* 21 USC § 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 pritioner, 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 pritioner. This traditional ivity is not the subject of this guidance.").
[4] Drug Quality and Security , 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 ," (December, 2013).