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DEPARTMENT OF HEALTH AND HUMAN SERVICE

Food and Drug Administration
New Orleans District
404 BNA Drive
Building 200, Suite 500
Nashville, TN 37217-1003

Telephone: 615-366-7801
Facsimile: 615-366-7802

June 24, 2008

WARNING LETTER NO. 2008-NOL-19

FEDERAL EXPRESS
DELIVERY SIGNATURE REQUESTED

Daniel A. Newman, President
Newman Inc., dba Medi-Stat
755-B McRae Avenue
Mobile, Alabama 36606

Dear Mr. Newman:

On December 4-7 and 14, 2007, a U.S. Food and Drug Administration (FDA) investigator inspected your facility, located at 755-B McRae Avenue, Mobile, Alabama. During the inspection, our investigator documented serious violations of the Federal Food, Drug, and Cosmetic Act (FDCA).

A. Compounded Drugs Under the FDCA and FDA's Regulatory Approach to Compounding

FDA's position is the FDCA establishes Agency jurisdiction over "new drugs," including compounded drugs. FDA's view is compounded drugs are "new drugs" within the meaning of 21 United States Code, Section 321(p) (21 USC 321), because they are not "generally recognized, among experts . . . as safe and effective" for their labeled uses [*See Weinberger v. Hynson, Westcott & Dunning,* 412 U.S. 609, 619, 629-30 (1973) (explaining the definition of "new drug")]. There is substantial judicial authority supporting FDA's position of which compounded drugs are not exempt from the new drug definition [*See Prof'ls & Patients for Customized Care v. Shalala,* 56 F.3d 592, 593 n.3 (5th Cir. 1995) ("Although the [FDCA] does not expressly exempt 'pharmacies' or 'compounded drugs' from the new drug . . . provisions, the FDA as a matter of policy has not historically brought enforcement actions against pharmacies engaged in traditional compounding."); *In the Matter of Establishment Inspection of: Wedgewood Village Pharmacy,* 270 F. Supp. 2d 525, 543-44 (D.N.J. 2003), *aff'd, Wedgewood Village Pharmacy v. United States,* 421 F.3d 263, 269 (3d Cir. 2005) ("The FDCA contains provisions with explicit exemptions from the new drug . . . provisions. Neither pharmacies nor compounded drugs are expressly exempted.")]. FDA maintains, because they are "new drugs"

under the FDCA, compounded drugs may not be introduced into interstate commerce without FDA approval.[1]

The drugs pharmacists' compound are rarely FDA-approved and thus lack an FDA finding of safety and efficacy. However, FDA has long recognized the important public health function served by traditional pharmacy compounding. FDA regards traditional compounding as the extemporaneous combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication tailored to the specialized needs of an individual patient [*See Thompson v. Western States Medical Center,* 535 U.S. 357, 360-61 (2002)]. Traditional compounding typically is used to prepare medications unavailable commercially, such as a drug for a patient who is allergic to an ingredient in a mass-produced drug or diluted dosages for children.

Through the exercise of enforcement discretion, FDA historically has not taken enforcement actions against pharmacies engaged in traditional pharmacy compounding. Rather, FDA has directed its enforcement resources against establishments whose activities raise the kinds of concerns normally associated with a drug manufacturer and whose compounding practices result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA.

FDA's current enforcement policy, with respect to the compounding of human drugs, is articulated in Compliance Policy Guide (CPG), Section 460.200 ["Pharmacy Compounding"], issued by FDA on May 29, 2002 [*See Notice of Availability*, 67 *Fed. Reg.* 39,409 (June 7, 2002)].[2] The CPG identifies factors FDA considers in deciding whether to initiate enforcement action with respect to compounding. These factors help differentiate the traditional practice of pharmacy compounding from the manufacture of unapproved new drugs. They further address compounding practices which result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA. As stated in the CPG,"[t]he . . . list of factors is not intended to be exhaustive."

B. Factual Background

Your firm purports to be a compounding pharmacy, but our investigation found your operation exceeds the practices associated with traditional, extemporaneous compounding. Your firm manufactures large volumes of standardized transdermal, prescription products ("KETO-STAT," "NEURO-STAT," "NEURO-DYSTONIA," "SHINGLES TDO," and "GOUT TDO") in anticipation of receiving prescriptions.

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[1] In August 2006, the U.S. District Court for the Western District of Texas issued a ruling in *Medical Center Pharmacy v. Gonzales* interpreting, among other things, the application of the "new drug" provisions of the FDCA to compounded drugs. *See Medical Center Pharmacy v. Gonzales,* MO-04-CV-130, (W.D. Tex, Aug. 30, 2006). The government has appealed this decision to the U.S. Court of Appeals for the Fifth Circuit. Pending resolution of this appeal, FDA is abiding by the district court's decision in the Western District of Texas and with respect to the plaintiffs covered by the decision.

[2] Although Section 503A of the FDCA (21 USC 353a) addresses pharmacy compounding, this provision was invalidated by the Ninth Circuit's ruling in *Western States Medical Center v. Shalala,* 238 F.3d 1090 (9th Cir. 2001), because Section 503A included unconstitutional restrictions on commercial speech and those restrictions could not be severed from the rest of 503A. In *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), the Supreme Court affirmed the Ninth Circuit ruling in which the provisions in question violated the First Amendment.

From September 1 to December 14, 2007, your firm produced [redacted] batches of standardized prescription drug products yielding approximately [redacted] with an average batch size of [redacted] Your firm dispenses these products in sizes varying from [redacted] which equates to a range of [redacted] per batch, respectively. In October 2007 your firm prepared [redacted] batches [redacted] of KETO-STAT, NEURO-STAT, and NEURO-DYSTONIA, and [redacted] batch sizes of NSAID and GOUT TDO [redacted] SHINGLES TDO is prepared [redacted] size. The production of this volume of standardized prescription drug products is inconsistent with traditional extemporaneous compounding, which involves compounding a medication based on specific medical needs of individually identified patients.

Your firm produces large volumes of drug products in anticipation of receiving prescriptions. On the first day of our inspection, your firm had the following quantity of drug products on hand: over [redacted] of KETO-STAT; over [redacted] of NEURO-STAT; over [redacted] of NEURO-DYSTONIA; over [redacted] of GOUT TDO; over [redacted] of SHINGLES TDO; and, over [redacted] of NSAID.

During the inspection, you stated approximately [redacted] of all finished drug products are distributed outside of Alabama, to the following states: [redacted] Your firm is engaged in the commercial-level distribution of standardized drug products. You employ a team of [redacted] sales representatives and contract the services of several other sales representatives to visit physician's offices, provide preprinted prescription pads and promotional material to physicians, and obtain "orders" from physicians for your transdermal, prescription drug products. Furthermore, your firm markets its transdermal products by providing physicians with drug product samples on their request.

Additionally, the labeling for your firm's transdermal products include the following claims for common uses:

"KETO-STAT" –

- "Osteoarthritis, bone and joint inflammation, rheumatism, tennis elbow, bone spurs, bone, joint and cartilage trauma"

"NEURO-STAT"

- "Athralgia [*sic*] with nueropathic [*sic*] involvement. Origin may be trauma, post-op or disease. Effective for fibromyalgia, neuroma, tmj, etc."

"NEURO-DYSTONIA"

- "Complicated neuropathic pain, used when other therapies are unsuccessful. Effective with skeletal muscle involvement. Chronic pelvic phantom pain, post herpetic neuralgia, vulvodynia, etc."

"SHINGLES TDO"

- "Effective, fast therapy for Herpes Zoster, Herpes Simplex, Herpes Vaginalis (cold sores, shingles, fever blisters)"

"GOUT TDO"

- "Joint trauma and inflammation with nerve involvement, gout, gouty arthritis and pain due to disease such as complicated bursitis"

FDA regards these claims as false and misleading. FDA is not aware of substantial evidence consisting of adequate and well-controlled clinical investigations supporting these claims.

Your firm's large production volume, marketing, and dispensing practices exceed the scope of traditional pharmacy compounding and are akin to a pharmaceutical manufacturer. As such, FDA will not exercise enforcement discretion with respect to your firm's drug production.

C. Violations of the FDCA

Unapproved New Drug Products

The products made by your firm are drugs within the meaning of Section 201(g) of the FDCA [21 USC 321(g)]. These products are new drugs as defined by Section 201(p) of the FDCA [21 USC 321(p)], because they are not generally recognized by qualified experts as safe and effective for their labeled uses. No approved application pursuant to Section 505 of the FDCA [21 USC 355] is in effect for these products. Accordingly, their introduction or delivery for introduction into interstate commerce violates Sections 505(a) and 301(d) of the FDCA [21 USC 355(a) and 331(d)]. A new drug may not be introduced or delivered for introduction into interstate commerce unless an FDA-approved application for it is in effect.

Misbranded Drug Products

Your firm's drug products are misbranded under Section 502(a) of the FDCA [21 USC 352(a)], as their labeling is false or misleading.

Your firm's drug products are misbranded under Section 502(f)(1) of the FDCA [21 USC 352(f)(1)], because their labeling fails to bear adequate directions for use and they are not exempt from this requirement under Title 21, *Code of Federal Regulations*, Part 201, Section 115 (21 CFR 201.115).

Your firm's drug products are also misbranded under Section 502(o) of the FDCA [21 USC 352(o)], because they are manufactured in an establishment not duly registered under Section 510 of the FDCA [21 USC 360], and the articles have not been listed as required by Section 510(j) of the FDCA [21 USC 360(j)]. Your facility is not exempt from registration and drug listing requirements under 21 CFR 207.10 or Section 510(g) of the FDCA [21 USC 360(g)].

Adulterated Drug Products

Your firm's drug products are adulterated under Section 501(a)(2)(B) of the FDCA [21 USC 351(a)(2)(B)], because the controls and procedures used in their manufacture, processing, packing, and holding do not conform to Current Good Manufacturing Practice (CGMP) regulations set forth in 21 CFR 210 and 211. On December 14, 2007, our investigator documented significant violations of CGMP regulations including, but not limited to, the following:

1. Failure to test or examine, as appropriate, each lot of components, drug product containers and closures, as required by 21 CFR 211.84(d)(2). Specifically, your firm does not conduct at least one specific identity test on each component and establish the reliability of the supplier's analysis through appropriate validation of the supplier's test results at appropriate intervals [Reference: Form FDA 483, Observation 3].

2. Failure to test each batch of drug product to determine conformance to final specifications, including identity and strength of each active ingredient, before release and distribution, as required by 21 CFR 211.165(a). Specifically, your firm does not conduct any finished product testing on batches of drug product before distribution [Reference: Form FDA 483, Observation 2].

3. Failure to ensure equipment used in the manufacturing and processing of drug product is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use, as required by 21 CFR 211.63. Specifically, the [redacted] commercial mixer and [redacted] mixer used to manufacture your drug products have not been qualified [Reference: Form FDA 483, Observation 1].

4. Failure to assure all drug products meet applicable standards of identity, strength, quality, and purity at the time of use by establishing an expiration date determined by appropriate stability testing, as required by 21 CFR 211.137(a). Specifically, your firm failed to conduct stability testing on your finished drug products to support assigned expiration dates [Reference: Form FDA 483, Observation 6].

5. Failure to establish a quality control unit which has the authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure no errors have occurred, as required by 21 CFR 211.22(a). Specifically, not all production records are reviewed and approved [Reference: Form FDA 483, Observations 3 and 4].

6. Failure to ensure batch uniformity by establishing master production and control records for each drug product, as required by 21 CFR 211.186(a). Specifically, your firm does not have drug master records for drug products manufactured, including KETO-STAT, NEURO-STAT, NEURO-DYSTONIA, SHINGLES TDO, KBL, KCYL, GOUT TDO, and NSAID [Reference: Form FDA 483, Observation 5].

7. Failure to identify drug products with a lot or control number that permits determination of the history of the manufacture and control of the batch, as required by 21 CFR 211.130(c).

Specifically, finished drug product lot numbers are not identified on the drug product containers [Reference: Form FDA 483, Observation 7].

8. Failure to prepare and maintain batch production and control records documenting each significant step in the manufacturing or processing of each batch of drug product, as required by 21 CFR 211.188(b)(3). Specifically, not all batch records have lot numbers for raw components used. For example, batch records for KETO-STAT, lots [redacted] and [redacted], do not document lot numbers of the raw components used. [Reference: Form FDA 483, Observation 9].

9 Failure to establish written procedures for the following processes:

   a. Receiving, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures, as required by 21 CFR 211.80(a) [Reference: Form FDA 483, Observation 8.1];

   b. Production and process controls to assure your drug products have the identity, strength, quality, and purity they are purported to have, as required by 21 CFR 211.100(a) and (b) [Reference: Form FDA 483, Observation 8.2];

   c. In-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch, as required by 21 CFR 211.110(a) [Reference: Form FDA 483, Observation 8.3];

   d. Labels, labeling, and packaging materials used for drug products, as required by 21 CFR 211.130 [Reference: Form FDA 483, Observation 8.4];

   e. Warehousing of drug products, as required by 21 CFR 211.142 [Reference: Form FDA 483, Observation 8.5];

   f. Distribution of drug products, as required by 21 CFR 211.150 [Reference: Form FDA 483, Observation 8.5];

   g. A testing program designed to assess the stability of your drug products, as required by 21 CFR 211.166(a) [Reference: Form FDA 483, Observation 8.7];

   h. Rejection of drug products failing to meet established standards or specifications and any other relevant quality control criteria, as required by 21 CFR 211.165(f) [Reference: Form FDA 483, Observation 8.8];

   i. The review of production, control, and distribution records to evaluate drug product quality standards and determine the need for changes in drug product specifications or manufacturing or control procedures, as required by 21 CFR 211.180(e) [Reference: Form FDA 483, Observation 8.9];

   j. Equipment maintenance, including cleaning and calibration, as required by 21 CFR 211.67(b) [Reference: Form FDA 483, Observation 8.10]; and,

k. The handling of all written and oral complaints regarding drug products, as required by 21 CFR 211.198(a) [Reference: Form FDA 483, Observation 8.11].

Though not documented on the Form FDA 483, our investigator reported your firm fails to test in-process materials for identity, strength, quality, and purity as appropriate, as required by 21 CFR 211.110(c). Furthermore, your firm also failed to establish written procedures for production and process control designed to assure your drug products have the identity, strength, quality and purity they are represented to possess, as required by 21 CFR 211.100(a). Specifically, process validation has not been conducted for any of your firm's drug products. Your firm failed to evaluate by record review, at least annually, the quality standards of each drug product to determine the need for changes in specifications, manufacturing, or control procedures, as required by 21 CFR 211.180(e).

In addition, your firm manufactures the hormone drug product [redacted] sublingual drops. When manufacturing potent compounds, you must conduct an adequate assessment of cross-contamination risks within your facility. Procedures and controls should be defined and implemented to prevent cross-contamination. Drug product operations and procedures must be performed in specifically defined areas of adequate size to prevent contamination or mix-ups, as required by 21 CFR 211.42(c). Adequate cleaning validation, including sampling and a cleaning protocol, is necessary to preclude possible contamination of other drug products by hormone drug products manufactured by your firm, as required by 21 CFR 211.67(a).

Your firm's drug products are in violation of Section 301(a) of the FDCA [21 USC 331(a)] because introduction or delivery for introduction into interstate commerce of adulterated or misbranded drug products is a prohibited act.

The violations cited in this letter are not intended to be an all-inclusive statement of violations existing at your facility, and they may not be limited to the above-cited drug products. It is your responsibility to ensure your facility is operating in full compliance with all applicable requirements of the FDCA and the implementing regulations.

You should take prompt action to correct these deficiencies, and you should establish procedures whereby such violations do not recur. Failure to do so may result in regulatory action without further notice, including seizure and/or injunction.

You should notify this office in writing, within 15 working days from receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step taken to prevent recurrence. You should include in your response documentation, such as protocols, procedures, test data, and other useful information, to assist us in evaluating your corrections. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be completed. You can find guidance and information regarding regulations through links at FDA's Internet website at http://www.fda.gov/oc/industry.

Please address your reply to Rebecca A. Asente, Compliance Officer, at the address above. If you have questions regarding the contents of this letter, please contact Ms. Asente at (504) 219-8818, extension 104.

Sincerely,

H. Tyler Thornburg
District Director
New Orleans District

Enclosure: Form FDA 483, dated December 14, 2007