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DEPARTMENT OF HEALTH AND HUMAN SERVICE

Food and Drug Administration
New Orleans District
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Nashville, TN 37217-1003

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September 28, 2007

WARNING LETTER NO. 2007-NOL-16

FEDERAL EXPRESS
OVERNIGHT DELIVERY

Patrick Willingham, President and CEO
Med-South Pharmacy, Inc., dba Partners In Care
25819 Canal Road
Orange Beach, Alabama 36561

Dear Mr. Willingham:

On December 20-21, 2006, a U.S. Food and Drug Administration (FDA) investigator conducted an investigation at your facility, located at 206A Oak Mountain Circle, Pelham, Alabama. This investigation was initiated in response to reports of injuries relating to betamethasone acetate/betamethasone sodium phosphate multi-dose injectable drug product, made by your firm. Additionally, on February 21-23, and March 2, 2007, a follow-up inspection was conducted at your firm. During both instances, our investigators 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 (USC) 321(p), 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 which are not available 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

On December 15, 2006, Consumer Complaint number 39633 was filed with the FDA involving an adverse event associated with the administration of betamethasone acetate/betamethasone sodium phosphate 6mg/ml injectable suspension made by your firm. The injection was given to the patient by a physician on December 7, 2006. On December 20-21, 2006, an FDA investigator conducted a follow-up investigation to the consumer complaint at Partners In Care, Pelham, Alabama. The investigation revealed your firm received at least 70 complaints associated with the use of betamethasone acetate/betamethasone sodium phosphate 6mg/ml

[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 U.S.C. § 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.

injectable suspension made by Partners In Care. The complaints included redness, large swollen areas, bruising at the injection site, rash, fever, and cellulitis, with some patients requiring intravenous antibiotics. On December 22, 2006, Partners In Care initiated a voluntary recall of two lots (11272006@13 and 12042006@9) of betamethasone acetate/betamethasone sodium phosphate 6mg/ml for injection in 10ml multi-dose vials. Your firm later revealed a new formulation had been implemented to "improve workflow", and an incorrect amount of benzalkonium chloride (BZK), used as a preservative, had been added to the product. Your master formulation called for [redacted] and your analysis showed [redacted] per [redacted] times the intended amount) was added to the affected lots.

Your firm produces large volumes of injectable products which are copies or essentially copies of FDA-approved, commercially available products, including, but not limited to:

- betamethasone acetate/betamethasone sodium phosphate 6 mg/ml ([redacted]) and 7 mg/ml ([redacted])[3];
- methylprednisolone acetate 40 mg/ml ([redacted]) and 80 mg/ml ([redacted])
- triamcinolone acetonide 40 mg/ml ([redacted]);
- dexamethasone acetate 8 mg/ml ([redacted]);
- testosterone cypionate 200 mg/ml ([redacted]);
- promethazine hydrochloride 50 mg/ml ([redacted]);
- brompheniramine maleate 10 mg/ml ([redacted])
- sodium carboxymethylcellulose 1% ([redacted])
- triamcinolone diacetate 40 mg/ml ([redacted]);
- medroxyprogesterone 150 mg/ml ([redacted]);
- testosterone cypionate 200 mg/ml ([redacted]); and,
- triamcinolone diacetate 40 mg/ml ([redacted]).

FDA is seriously concerned about the public health risks associated with the large-scale production of injectable drugs which are copies or essentially copies of FDA-approved, commercially available products manufactured by firms not meeting the laws and regulations applicable to drug manufacturing. Your firm's typical batch sizes for these injectable drug products range from [redacted], which equates to as many as [redacted]) per batch, with an average of [redacted] batches of sterile injectable drugs manufactured daily. From January 1 to December 31, 2006, your firm produced a total of [redacted] batches of sterile injectable drug products yielding approximately [redacted]). The production of this volume of FDA-approved, commercially available products is inconsistent with traditional pharmacy compounding, which involves compounding medications not commercially available, based on specific needs of individually identified patients.

Your firm purports to be a compounding pharmacy, but your firm's operation exceeds the scope of traditional pharmacy practice. During the inspection, the pharmacist in charge stated approximately [redacted] of all finished injectable drug products are distributed into interstate commerce. You also utilize a team of [redacted] sales representatives to obtain "orders" for your injectable drug products from physicians' offices. The large volume of your firm's injectable drug products which are copies or essentially copies of FDA-approved, commercially available products, and your firm's dispensing practices for these products exceed the scope of traditional

[3] The parentheses in this and the following entries indicate the number of [redacted] produced in 2006, according to your records.

pharmacy compounding and are akin to a pharmaceutical manufacturer. As such, the FDA will not exercise enforcement discretion with respect to your firm's production of these drugs.

C. Violations of the FDCA

Unapproved New Drug Products

The injectable 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)].

Misbranded Drug Products

Your firm's injectable 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 injectable drug products are 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)].

Further, your firm's betamethasone acetate/betamethasone sodium phosphate 6mg/ml injectable suspension product (lot numbers 11272006@13 and 12042006@9) are misbranded within the meaning of Section 502(j) of the FDCA [21 USC 352(j)] because they are dangerous to health when used in the manner suggested by their labeling. Specifically, the affected lots contained [redacted] times the concentration of preservative than what was intended according to your new formulation.

Adulterated Drug Products

Your firm's injectable 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 the manufacture, processing, packing, and holding of the drug products do not conform to Current Good Manufacturing Practice (CGMP) regulations set forth in 21 CFR 210 and 211. On March 2, 2007, our investigator documented significant violations of CGMP regulations including, but not limited to, the following:

1. Failure to establish and follow written procedures to prevent microbiological contamination of injectable drug products purporting to be sterile, as required by 21 CFR 211.113(b). Specifically, your firm's manufacturing process has not been validated for your injectable drug products. In addition, the filters used to sterilize injectable drug products have not

been tested for integrity; smoke studies have not been conducted in the critical areas; and, particulate matter is not being monitored. The autoclave cycles used to terminally sterilize injectable suspension drug products have not been validated and there is no verification of their effectiveness with biological indicators [Reference: Form FDA 483, Observations 3 and 4].

2. Failure to test each batch of injectable drug product purporting to be sterile and/or pyrogen-free to determine conformance to such requirements, as required by 21 CFR. 211.167(a). Specifically, your firm tests finished injectable drug products for sterility on a monthly basis only [Reference: Form FDA 483, Observation 1].

3. Failure to ensure all components and injectable drug product containers and closures are, at all times, handled and stored in a manner to prevent contamination, as required by 21 CFR 211.80(b). Specifically, on February 21 and 22, 2007, our investigator documented empty, open, sterilized glass vials, which were exposed to environmental contamination in your Class 10,000 (ISO 7) room and Class 100,000 (ISO 8) ante room [Reference: Form FDA 483, Observation 16].

4. Failure to test each batch of injectable 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 product testing on all batches of injectable drug product prior to release. Currently, your firm conducts testing on the concentration of the active ingredient for injectable drug products on a monthly basis only [Reference: Form FDA 483, Observation 2].

5. Failure to reject injectable drug product which failed to meet established standards or specifications and any other relevant quality control criteria, as required by 21 CFR 211.165(f). Specifically, your firm distributed methylprednisolone acetate 80mg/ml, Lot number 09182006@2 of 1, which failed to meet the established assay specifications. The lot was distributed without conducting any reprocessing or any other further action. The concentration of methylprednisolone acetate in this lot was 92.02 mg/ml ( ] percent of the expected amount) [Reference: Form FDA 483, Observation 5].

6. Failure to establish and follow written procedures for production and process controls to assure your injectable drug products have the identity, strength, quality, and purity they are purported to have, as required by 21 CFR 211.100(a) and (b). Specifically, your firm has not established complete written procedures for the methods used to manufacture injectable drug products. The PCCA-provided "Logged Formula Worksheets" used by your firm for formulation of the sterile injectable products do not include complete manufacturing instructions and the instruction to use Sterile Water for Injection is not followed [Reference: Form FDA 483, Observations 19 and 20].

7. Failure to establish laboratory controls, including scientifically sound and appropriate specifications, standards, sampling plans and test procedures designed to assure the drug products conform to appropriate standards of identity, strength, quality and purity, as required by 21 CFR 211.160(b). Specifically, your firm has not established written specifications for finished injectable drug products [Reference: Form FDA-483, Observation 20].

8. Failure to establish a quality control unit which has the responsibility and 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 or, if errors have occurred, they have been fully investigated, as required by 21 CFR 211.22(a). Specifically, your firm has no designated quality control unit [Reference: Form FDA 483, Observation 7].

9. Failure to verify the identity of each component of injectable drug product and its conformance with all appropriate written specifications for purity, strength, and quality, as required by 21 CFR 211.84(d)(2). Specifically, your firm does not conduct any testing on injectable drug components upon receipt, nor does your firm obtain a certificate of analysis for each component received [Reference: Form FDA 483, Observation 18].

10. Failure to conduct and document a thorough investigation of any unexplained discrepancy or failure of a drug product to meet its specifications or to extend the investigation to other batches which may have been associated with the particular failure or discrepancy, as required by 21 CFR 211.192. Specifically, your firm failed to conduct complete root cause investigations for three complaints involving injectable drug products which could not be drawn into the syringe or discharged from the syringe. The complaints involved: dexamethasone acetate LA 8 mg/ml, Lot number [redacted] (dated October 23, 2006); triamcinolone diacetate 40 mg/ml, Lot number [redacted] (dated November 15, 2006); and, methylprednisolone acetate 40 mg/ml, Lot number [redacted] (dated January 27, 2007). In addition, none of the investigations were extended to other lots of product potentially impacted. [Reference: Form FDA 483, Observation 8].

11. Failure to assure all injectable 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 injectable drug products to support your assigned six-month expiration date [Reference: Form FDA 483, Observation 25].

12. Failure to establish a written testing program designed to assess the stability of your injectable drug products, as required by 21 CFR 211.166(a). Specifically, your firm lacked a program for, and failed to conduct stability testing on, your injectable drug products [Reference: Form FDA 483, Observation 23].

13. Failure to ensure all injectable drug products, set aside and held in unlabeled conditions, are sufficiently identified to preclude mislabeling, as required by 21 CFR 211.130(b). Specifically, on February 22, 2007, our investigator documented four trays of unidentified glass vials containing drug products on two different occasions in the compounding room [Reference: Form FDA 483, Observation 9].

14. Failure to prepare batch production and control records for each batch of drug product containing complete information relating to the production and control of each batch, including documentation where each significant step in the manufacturing, processing, packing, or holding of your injectable drug products was accomplished, as required by 21 CFR 211.188(b). Specifically, mixing and sonicator times, heating temperatures, and drug product pH prior to filling are not recorded. In addition, batch records for sterile injectable drug products lack both specific identification, such as lot codes, for the drug product

containers and closures used and specimens of finished product labeling [Reference: Form FDA 483, Observations 15, 19 and 24].

15. Failure to establish written procedures for cleaning and maintenance of equipment used in the manufacture, processing, packing, or holding of a drug product, as required by 21 CFR 211.67(b). Specifically, your firm does not have any written cleaning procedures [Reference: Form FDA 483, Observation 14].

16. Failure to establish written procedures describing in sufficient detail the receipt, 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). Specifically, your firm has no written procedures to describe in detail the receipt, identification, storage, handling, sampling, testing, approval, and rejection of components, injectable drug product containers, and closures [Reference: Form FDA 483, Observation 17].

17. Failure to routinely calibrate automatic, mechanical, or electronic equipment according to a written program designed to assure proper equipment performance, as required by 21 CFR 211.68(a). Specifically, your firm routinely does not calibrate scales, the autoclave, or sonicators used to manufacture injectable drug products. In addition, your firm does not have any written procedures addressing equipment calibration [Reference: Form FDA 483, Observation 13].

18. Failure to calibrate instruments at suitable intervals in accordance with an established written program, as required by 21 CFR 21.160(b)(4). Specifically, your firm routinely does not calibrate pH meters. In addition, your firm does not have any written procedures addressing instrument calibration [Reference: Form FDA-483, Observation 13].

19. Failure to establish written procedures describing in sufficient detail the control procedures employed for the issuance of labeling, as required by 21 CFR 211.125(f). Specifically, your firm does not have any written procedures describing labeling processes [Reference: Form FDA 483, Observation 21].

20. Failure to retain and store, under conditions consistent with product labeling, reserve samples which are representative of each lot or batch of finished injectable drug product, as required by 21 CFR 211.170(b). Specifically, your firm does not maintain finished injectable drug product reserve samples [Reference: Form FDA 483, Observation 22].

21. Failure to establish a written record of major equipment cleaning, maintenance, and use, as required by 21 CFR 211.182. Specifically, your firm failed to maintain individual equipment logs documenting the date, time, product, and lot number of each batch of finished injectable drug product processed [Reference: Form FDA 483, Observation 26].

22. Failure to ensure employees engaged in manufacturing, processing, packing, or holding of a drug product shall have education, training, including training in CGMPs, and experience, or any combination thereof, to enable the person to perform the assigned functions. Employees involved in the manufacturing of your injectable drug products have not been trained in CGMP, as required by 21 CFR 211.25(a) [Reference: Form FDA 483, Observation 10].

23. Failure to reject components which fail to meet required specifications, as required by 21 CFR 211.84(e). Specifically, although your formula worksheets require the use of sterile water for injection in your sterile injectable drug products, your firm uses a component labeled as "Sterile Water for Irrigation USP" and "Not for Injection" to manufacture these drug products. Your firm does not have documentation certifying each lot of the component labeled "Sterile Water for Irrigation USP" meets specifications for sterile water for injection [Reference: Form FDA 483, Observation 6].

24. Failure to calculate actual yields and percentages of theoretical yield at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of your injectable drug products, as required by 21 CFR 211.103 [Reference: Form FDA 483, Observation 11].

Your firm's injectable 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. FDA will not exercise enforcement discretion with regard to these and the other violations cited in this letter.

It is our understanding, your firm is also compounding non-injectable products which may be copies or essentially copies of FDA-approved, commercially available products, including, but not limited to, lorazepam 2 mg/ml solution, progesterone 200 mg capsules, promethazine 25mg suppositories, promethazine 25 mg capsules, carbidopa/levodopa 25/100 mg suspension, hydromorphone 8mg capsules, and fentanyl 400 mcg troches. Because these products are copies of FDA-approved, commercially available products, FDA will not exercise enforcement discretion. For the remaining products, which are essentially copies of FDA-approved, commercially available products, FDA will not exercise enforcement discretion unless your firm can demonstrate a patient-specific medical need for the variation, as determined by the prescribing healthcare provider.

The above deficiencies should not be construed as an all-inclusive list of violations that may exist 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 violations, 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 procedures or 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 March 2, 2007

cc: [redacted]
Med-South Pharmacy, Inc., dba Partners In Care
206A Oak Mountain Circle
Pelham, Alabama 35124