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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Dallas District
4040 North Central Expressway
Dallas, Texas 75204-3128

April 13, 2007

Ref: 2007-DAL-WL-14

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. David N. Jonas, Chairman/CEO
PharMEDium Services, LLC
Two Conway Park
150 North Field Drive, Ste 350
Lake Forest, IL 60045

Dear Mr. Jonas:

This Warning Letter concerns compounding activities performed by PharMEDium Services, LLC ("PharMEDium"). In particular, this Warning Letter concerns: (1) PharMEDium's compounding of Magnesium Sulfate ($MgSO_4$) in Dextrose Injection, United States Pharmacopeia (USP), at its Houston, TX, facility; and (2) FDA's inspectional findings of PharMEDium's compounding practices for sterile products at its Cleveland, MS, facility.

The $MgSO_4$ in Dextrose Injection, USP, the 2 mcg/ml Fentanyl Citrate and 0.125% Bupivacaine HCl in 0.9% NaCl, and the 1 mg/ml Morphine Sulfate in 0.9% NaCl products made by PharMEDium are drugs within the meaning of section 201(g) of the Federal Food, Drug, and Cosmetic Act (FDCA) [21 U.S.C. § 321(g)]. These products are new drugs under section 201(p) of the FDCA [21 U.S.C. § 321(p)], because they are not generally recognized by qualified experts as safe and effective for their labeled uses. As discussed below, these drugs and your production and distribution of these drugs violate the FDCA.

A. Compounded Drugs Under the FDCA and the Food and Drug Administration's (FDA) Regulatory Approach to Compounding

FDA's position is that the Federal Food, Drug, and Cosmetic Act (FDCA) establishes agency jurisdiction over "new drugs," including compounded drugs. FDA's view is that compounded drugs are "new drugs" within the meaning of 21 U.S.C. § 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 that 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 that, because they are "new drugs" under the FDCA, compounded drugs may not be introduced into interstate commerce without FDA approval.[1]

The drugs that 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 that 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 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 that the Agency 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 that result in

[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 filed a notice of appeal to the U.S. Court of Appeals for the Fifth Circuit. The district court's ruling only applies in the Western District of Texas.

[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), that 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 that the provisions in question violated the First Amendment.

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." See CPG section 460.200 ["Pharmacy Compounding"].

B. Factual Background

Among other things, your firm receives concentrated drugs packaged in bulk, which require further dilution with other pharmaceutical ingredients for parenteral use. For example, the PharMEDium facility located in Houston, TX, produces, labels, and distributes to hospitals and healthcare facilities approximately [redacted] units annually of parenteral solutions. These solutions are prepared in anticipation of your firm receiving routine orders from hospitals and medical facilities that provide patient care.

1. Houston, TX Facility

On March 18-31, 2005, FDA, together with the Texas State Board of Pharmacy (TSBP), inspected PharMEDium Services, LLC, 7525 South Freeway, Houston, TX. The Houston facility is licensed by the Texas State Board of Pharmacy as a compounding pharmacy. The inspection was a follow-up to a notification by the New Jersey Department of Health and Senior Services and the Centers for Disease Control and Prevention (CDC) of a potential *Serratia marcescens* infection in a patient at a hospital in [redacted] NJ, following the administration of $MgSO_4$ in Dextrose Injection, USP compounded by PharMEDium Services, LLC, Houston, TX.

On March 18, 2005, FDA collected a sample of $MgSO_4$ in Dextrose Injection, USP from the hospital in [redacted] NJ, where five patients exhibited signs and symptoms of sepsis after receiving this product. This sample contained several units from several lots of your drug product that was shipped to this hospital. Hospital records confirmed that one of the patients received an intravenous infusion of $MgSO_4$ in Dextrose Injection, USP from lot #100504900049 (Exp. 04/04/05),[3] one of the six lots of this product that your firm distributed to the hospital. Lot #100504900049 was compounded at your facility in Houston, TX. FDA's laboratory tested 20 intact units of this lot and found that 3 units were contaminated with *Serratia marcescens*. Our results were independently confirmed by the hospital laboratories and the New Jersey Department of Health and Senior Services.

The FDA also conducted a follow-up investigation in April 2005, at a hospital in [redacted] South Dakota, regarding the death of a patient who received $MgSO_4$ in Dextrose Injection, USP compounded by your firm. On March 27, 2005, the patient, who was recovering from surgery, was administered one dose of your product. Within hours of the dosing, the patient exhibited signs and symptoms of sepsis. The hospital laboratory cultured blood samples from the patient and determined the presence of *Serratia marcescens*. As a result, FDA collected 18 units from the four lots of your firm's $MgSO_4$ in Dextrose Injection, USP that were present at the hospital. Our analysis revealed that

[3] $MgSO_4$ in Dextrose Injection, USP, Compounded Magnesium Sulfate 1g (2 ml 50% injection) added to 50 ml 5% Dextrose Injection USP, Lot #100504900049 (Exp. 04/04/05).

2 of 10 intact units (sub-sample #1 and #12) from lot #100506800034 (Exp 04/23/05),[4] compounded at your facility in Houston, TX, were contaminated with microbial growth. Sub-sample #1 was contaminated with *Pseudomonas aeruginosa, Alcaligenes xylosoxidans subspecies denitrificans, Chromobacterim violaceum,* and *Acinetobacter lwoffii.* Sub-sample #12 was contaminated with *Pseudomonas aeruginosa* and *Chromobacterium violaceum.*

2. Cleveland, MS Facility

On January 17, 2006, FDA received a report pertaining to an adverse event at [redacted] in [redacted] AZ, relating to a product that was produced at PharMEDium's Cleveland, MS, site. According to the report, on January 11, 2006, a patient was administered a product that, based on the labeling of the product, was believed to be an epidural injection of 2mcg/ml Fentanyl Citrate and 0.125% Bupivacaine HCL (lot #053570083). The patient showed signs and symptoms of decreased consciousness, hypoxia, and hypotension. The medical center's toxicology lab tested multiple unopened samples of the epidural injections (including samples from lot #053570083), and the tests revealed the presence of Morphine Sulfate. Fentanyl/Bupivacaine was not detected in any of the samples. Your firm determined that the product labeled Fentanyl/Bupivacaine actually contained Morphine Sulfate. The hospital's investigation also revealed that a product made at your Cleveland, MS, site and labeled as containing Morphine Sulfate actually contained Fentanyl/Bupivacaine. Both the Fentanyl/Bupivacaine and the Morphine Sulfate products were made at your Cleveland, MS site on December 23, 2005. A Class I recall of the Fentanyl/Bupivacaine and the Morphine Sulfate products was initiated by your firm on January 12, 2006.

FDA conducted an inspection of your Cleveland, MS site on January 25-27, 2006. A Form FDA-483 was issued citing several significant inspectional observations involving your Quality Assurance unit and your labeling and packaging operations.

C. Adulterated and Misbranded Products – *Houston, TX*

1. Adulteration Under Section 501(a)(1) [21 U.S.C. § 351(a)(1)]

PharMEDium's $MgSO_4$ in Dextrose Injection, USP products are adulterated under section 501(a)(1) of the FDCA [21 U.S.C. § 351(a)(1)] in that they consist in whole or in part of a filthy, putrid, or decomposed substance as evidenced by the presence of *Serratia marcescens, Pseudomonas aeruginosa, Alcaligenes xylosoxidens subspecies denitrificans, Chromobacterim violaceum* and *Acinetobacter lwoffii.*

2. Adulteration Under Sections 501(a)(2)(A) and 501(a)(2)(B) [21 U.S.C. §§ 351(a)(2)(A) and 351(a)(2)(B)]

[4] $MgSO_4$ in Dextrose Injection, USP, Compounded Magnesium Sulfate 2g (4 ml 50% injection) added to 50 ml 5% Dextrose Injection USP, Lot #100506800034 (Exp. 04/23/05).

The $MgSO_4$ in Dextrose Injection, USP produced at your Houston, TX, facility are adulterated within the meaning of section 501(a)(2)(A) of the FDCA [21 U.S.C. § 351(a)(2)(A)] in that they are prepared, packed, or held under insanitary conditions whereby they may be contaminated with filth, or whereby they may be rendered injurious to health. Additionally, the $MgSO_4$ in Dextrose Injection, USP products are adulterated within the meaning of section 501(a)(2)(B) of the FDCA [21 U.S.C. § 351(a)(2)(B)] because the methods used in, or the facilities or controls used for, the preparation of these sterile compounded drug products do not comply with current good manufacturing practice to assure that these drug products meet the requirements of the FDCA as to safety and that these products have the identity and strength, and meet the quality and purity characteristics, which they purport or are represented to possess.

FDA conducted an inspection of your Houston facility in March 2005. The observations from this inspection were listed on the Form FDA-483 (Inspectional Observations) that was issued to and discussed with Mr. Richard Dillow, Center Manager, in the presence of Mr. Richard Kruzynski, President, at the conclusion of the inspection. We have reviewed your firm's response to the FDA-483, dated April 14, 2005, and have the following comments:

Observation #1 from the FDA-483 states that your firm did not determine an assignable cause for any of the [redacted] instances since March 2004 where your product exceeded your action level for viable microorganisms of [redacted] Colony Forming Units (CFU). Please note that, as a standard practice, members of the pharmaceutical community utilize 1 CFU as the environmental monitoring level of critical surface areas. The observation also notes that your investigation did not determine whether each excursion (i.e., an event where an alert or action limit has been exceeded) adversely affected the lots of drug product that were made on the days the excursions occurred. In your response, you state that, for each excursion, the immediate area of operation within the respective hoods was re-tested and passed the established acceptance criteria. You also state that a trend analysis for each excursion did not indicate that a system failure had occurred. However, we believe that your investigation should attempt to identify potential causes for each excursion. Determining potential causes will assist you in implementing adequate measures to prevent further excursions, and your investigation should determine whether there was any impact on any lots manufactured during the excursions.

Observation #2 from the FDA-483 states that your firm utilized a revolving schedule for the placement of air settling plates in the [redacted] Laminar Flow Hoods (LAH) during compounding operations. However, per this schedule, your firm often placed settling plates within LAHs that were not used for sterile compounding operations on that specific day. Your response, indicating that Standard Operating Procedure (SOP) # CPS-707, *Microbiological Environmental Monitoring Testing*, has been changed to require placement of air settling plates in hoods actively being used in compounding, appears satisfactory, but will need to be evaluated by FDA during the next inspection of your facility.

Observation #3 from the FDA-483 states that there was no documentation that your firm performed a visual, unit-by-unit examination of containers, vials, and ampoules for defects. You also did not visually inspect each component, diluent, or product for visible

contamination. Your response, indicating that SOP # CPS-504, *Preparation of Additives*, has been changed to require documentation of visual examination of sterile components, diluents, and products, as well as containers and closures for use in compounded solutions, appears satisfactory but will need to be evaluated by FDA during the next inspection of your facility.

Observation #4 from the FDA-483 states that there was no assurance that the alcohol in the sterile pads utilized during sterile compounding was, in fact, sterile filtered. These alcohol pads are used to sanitize injection ports prior to performing the sterile compounding operations. Your response, indicating that PharMEDium has and continues to pursue a source of sterile filtered alcohol prep pads, appears to be a satisfactory effort to improve the quality of your systems and the integrity of your IV solutions. In addition, during a teleconference between your firm and FDA on August 4, 2005, you stated that your firm has implemented a new two-stage cleaning process to further assure the elimination of viable microorganisms as well as spores. Your corrective actions appear adequate but will need to be evaluated by FDA during the next inspection of your facility.

3. **Misbranding Under Sections 502(a) and 502(j) [21 U.S.C. §§ 352(a) and 352(j)]**

The $MgSO_4$ in Dextrose Injection, USP products made by your firm are misbranded within the meaning of section 502(a) of the FDCA [21 U.S.C. § 352(a)] because their labeling is false or misleading. The products are further misbranded within the meaning of section 502(j) of the FDCA [21 U.S.C. § 352(j)] because they are dangerous to health when used in the manner suggested by their labeling.

PharMEDium's $MgSO_4$ in Dextrose Injection, USP products are used parenterally. Parenteral products purport to be sterile and the labeling for your $MgSO_4$ in Dextrose Injection, USP products indicates that they were for parenteral use. Further, your $MgSO_4$ in Dextrose Injection, USP products were compounded by adding 1 ml or 2 ml of Magnesium Sulfate Injection, USP (50%) to 50 ml 5% Dextrose Injection, USP single dose containers. Your firm then affixes its labeling to the 5% Dextrose Injection, USP 50 ml containers. After receiving an order, the applicable manufacturer's package insert for Magnesium Sulfate Injection, USP (50%) is placed in the shipping carton with the finished product. Both the 50 ml 5% Dextrose Injection, USP single dose container labels and the package insert for Magnesium Sulfate Injection, USP (50%) read, in pertinent part, "STERILE."

As noted above, FDA laboratory testing found that several lots of MgSO4 in Dextrose Injection drugs produced by PharMEDium at the facilities in Houston, TX were contaminated with several different species of microorganisms. Thus, the products' labeling is false and misleading because these solutions were not in fact sterile for their intended use. In addition, these products are dangerous to health when used parenterally. Therefore, the contaminated drugs are misbranded under Sections 502(a) and 502(j) of the FDCA [21 U.S.C. §§ 352(a) and 352(j)].

D. **Adulterated and Misbranded Products – *Cleveland, MS***

1. Adulteration Under Section 501(a)(2)(B) [21 U.S.C. § 351(a)(2)(B)]

The 2 mcg/ml Fentanyl Citrate and 0.125% Bupivacaine HCl in 0.9% NaCl and the 1 mg/ml Morphine Sulfate in 0.9% NaCl products made at your Cleveland, MS site are adulterated within the meaning of section 501(a)(2)(B) of the FDCA [21 U.S.C. § 351(a)(2)(B)] because the methods used in, or the facilities or controls used for, the preparation of these sterile drug products do not comply with current good manufacturing practice to assure that these drug products meet the requirements of the FDCA as to safety and that these products have the identity and strength, and meet the quality and purity characteristics, which they purport or are represented to possess.

FDA conducted an inspection of your Cleveland, MS facility on January 25-27, 2006, and documented significant violations from the acceptable standards for the preparation of sterile drugs. The observations were listed on the Form FDA-483 (Inspectional Observations) that was issued to and discussed with Mr. Reginald C. Funches, Quality Manager, at the conclusion of the inspection. We have reviewed your firm's written response to the Form FDA-483 observations, dated February 14, 2006, and have the following comments:

Observation #2 states that your firm failed to establish, in writing, a Quality Assurance program that identifies the individual(s) with the responsibility and authority to approve or reject all components, drug product containers, in-process tests, packaging material, labeling, and finished product release of sterile drug products. Specifically, production technicians, who are not employees of the quality department, are given authority to approve and release labeling for use during the packaging and labeling of finished products. In your written response, you state that, "PharMEDium Services does have Quality checks written in our procedures." However, your response did not address the inspectional observation, in that you did not state that there are written procedures under a formal Quality Assurance program to show that the production technician was authorized to release the labeling for use during packaging and labeling of finished products, nor did you document that the production technician had adequate qualifications or training to perform such tasks. We expect that production technicians are authorized, skilled, educated, and have the appropriate training to approve and release labeling and to ultimately approve and release drug products.

Observation #4 states that in-process product is not adequately labeled in that the material is not always identified. Our investigator observed unlabeled finished product that was maintained in unlabeled totes. Only one tote contained an identifying label, which was not affixed to the tote. Failure to exercise strict control over packaging and labeling operations, including proper identification of an in-process product, can lead to labeling mix-ups. In your written response, you state that as of January 30, 2006, every tote is now labeled for each batch and affixed to the tote in a manner to address the concerns of a label being lost or removed. Your written response does not state whether any standard operating procedures were revised or whether production personnel were (re)trained. Please provide comments on all of your firm's corrective

and preventive actions regarding this observation, including whether procedures (if any) were revised or if employees were (re)trained.

Observation #8 states that your line clearance activities are inadequate in the labeling and pouching area in that plastic bins containing package inserts of multiple drug products are kept in each station at all times. Failure to exercise strict control over labeling issued, including return of unused package inserts to inventory, can lead to labeling mix-ups. Our investigator observed unused package inserts remaining on production lines after line clearance activities had been completed. In your written response, you state that "the package inserts were removed immediately from each packing workstation and are now in a separate location." You have also changed your standard operating procedure (CPS-621, issue date February 14, 2006, section 5.25.14) to reflect this change. Your response appears satisfactory with the exception of stating whether your operating personnel were (re)trained on the new procedure. Please provide comments on all of your firm's corrective and preventive actions regarding this observation, including whether employees were (re)trained on the updated procedure.

Observation #9 addresses your firm's failure to initiate an investigation into production deviations upon an event occurring when the quality assurance staff were not present (i.e., [redacted]). Our investigator noted that two in-process lots (5mg/ml Morphine Sulfate cassettes lot #060250094 and 0.2 mg/ml Hydromorphone 25 ml syringe lot # 060250036) were observed in a quarantine area, but review of the accompanying batch production records did not reveal the reason for their quarantine status. Failure to fully document the reason a product is placed in quarantine status can lead to an inadequate investigation and could hamper the appropriate corrective and preventative action. Your written response states that "A change was made to ensure that a quarantine report is initiated at the time a batch deviation occurs to ensure that the batch records does [sic] reveal the reason for quarantine status." This change is reflected in your SOP (CPS-621, issue date February 14, 2006, section 5.26.2 and section 5.28). Your written response appears satisfactory with the exception of stating if your operating personnel were (re)trained on the new procedure. Please provide comments on all of your firm's corrective and preventative actions regarding this observation, including whether employees were (re)trained on the updated procedure.

At this time, your written responses to inspectional observations 1, 3, 5, 6, and 7, appear adequate. Your corrective and preventative actions for all inspectional observations will be evaluated by FDA during the next inspection of your Cleveland, MS site.

2. **Misbranding Under Sections 502(a) and 502(j) [21 U.S.C. §§ 352(a) and 352(j)]**

The 2 mcg/ml Fentanyl Citrate and 0.125% Bupivacaine HCl in 0.9% NaCl and the 1 mg/ml Morphine Sulfate in 0.9% NaCl products made by your firm are misbranded within the meaning of section 502(a) of the FDCA [21 U.S.C. § 352(a)] because their labeling is false

or misleading. The products are further misbranded within the meaning of section 502(j) of the FDCA [21 U.S.C. § 352(j)] because they are dangerous to health when used in the manner suggested by their labeling.

Your firm's 2 mcg/ml Fentanyl Citrate and 0.125% Bupivacaine HCl in 0.9% NaCl (lot #053570083) was labeled to contain 2 mcg/ml Fentanyl Citrate and 0.125% Bupivacaine HCl in 0.9% NaCl. Laboratory analysis showed this product (lot #053570083) to contain morphine sulfate. Your firm initiated a voluntary recall of your 2 mcg/ml Fentanyl Citrate and 0.125% Bupivacaine HCl in 0.9% NaCl (lot #053570083) and 1 mg/ml Morphine Sulfate in 0.9% NaCl (lot #053570081) because the labels of these two products were mistakenly interchanged (i.e.: 2 mcg/ml Fentanyl Citrate and 0.125% Bupivacaine HCl in 0.9% NaCl was labeled as 1 mg/ml Morphine Sulfate in 0.9% NaCl, and vice versa). Thus, these products are misbranded because their labeling is false and misleading and dangerous to health when used in a manner suggested by their labeling.

E. Conclusion

Neither this letter nor the observations noted on the Forms FDA 483 are intended to be an all-inclusive list of the deficiencies that may exist at your facilities. It is your responsibility to ensure that your operations are in full compliance with all applicable requirements of the FDCA and the implementing regulations. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct all of the violations noted in this letter, and you should establish procedures whereby such violations do not recur. Failure to promptly correct violations may result in regulatory action without further notice, including seizure and/or injunction.

Please notify this office within 15 working days of receipt of this letter, stating the action that you will take to correct the noted violations, including an explanation of the steps taken to prevent their recurrence. Your response should demonstrate your assurance that corrections will also be put in place at other PharMEDium facilities conducting similar prescription drug compounding and distribution activities.

You should address your reply to this letter to the U.S. Food and Drug Administration, Attention: Jim Lahar, Compliance Officer, at the above address. If you have any questions about this letter, you may contact Mr. Lahar at (214) 253-5219.

Sincerely,

Michael A. Chappell
Director, Dallas District