DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region

Food and Drug Administration
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WARNING LETTER

October 31, 2006

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. John Scott Karolchyk, R.Ph.
Mr. Bernard Covalesky, R.Ph.
Co-Owners
Pharmacy Creations
540 Route 10 West
Randolph, New Jersey 07869

07-NWJ-02

Dear Mssrs. Karolchyk and Covalesky:

On January 17-February 8, 2006, investigators from the U.S. Food and Drug Administration (FDA) inspected your firm, Pharmacy Creations, located at 540 Route 10 West Randolph, New Jersey. This inspection revealed that your firm produces human and animal prescription drugs in various dosage forms and strengths. The inspection also revealed serious violations of the Federal Food, Drug, and Cosmetic Act (FDCA).

The products made by your firm are drugs within the meaning of section 201(g) of the 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)] and new animal drugs under section 201(v) of the FDCA [21 U.S.C. § 321(v)] because they are not generally recognized by qualified experts as safe and effective for their labeled uses. As discussed below, these new drugs and new animal drugs, and your production and distribution of them, violate the FDCA.

A. Compounded Drugs Under the FDCA and FDA's 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.

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 product, 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 policies with respect to the compounding of human drugs and compounding of drugs for use in animals are articulated in two Compliance Policy Guide (CPGs). 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)) addresses the compounding of human drugs.[1] CPG section 608.400 ["Compounding of Drugs for Use in Animals"], issued in revised form by FDA's Center for Veterinary Medicine on July 8, 2003, addresses the compounding of drugs for use in animals.

These CPGs identify 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 and unapproved new animal drugs. They further address compounding practices that result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA. As stated in the CPGs, the factors listed in the CPGs are not intended to be exhaustive. *See* CPG section 460.200 ["Pharmacy Compounding"] ("The . . . list of factors is not intended to be exhaustive.") and CPG section 608.400

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[1] The status of Section 503A of the FDCA ["Pharmacy Compounding"] [21 U.S.C. § 353a] was addressed by the Supreme Court in *Thompson v. Western States Medical Center,* 535 U.S. 357 (2002).

["Compounding of Drugs for Use in Animals"] ("The . . . list of factors is not intended to be all inclusive."

1. CPG on Compounding of Human Drugs [CPG, Section 460.200]

CPG, section 460.200, addresses the factors that the agency considers in determining whether to initiate enforcement action with respect to the compounding of human drugs. Some of the factors identified in the CPG on human compounding include considering whether a firm:

- compounds drugs in anticipation of receiving prescriptions, except in very limited quantities, in relation to the amounts of drugs compounded after receiving valid prescriptions;
- compounds finished drugs from bulk active ingredients that are not components of FDA approved drugs, without an FDA sanctioned investigational new drug application (IND);
- compounds drugs that were withdrawn or removed from the market for safety reasons;
- compounds drugs that are copies, or essentially copies, of commercially available FDA-approved drug products without documented patient-specific medical need.

2. CPG on Compounding of Drugs for Use in Animals [CPG, section 608.400]

CPG, section 608.400, addresses the factors that the agency considers in determining whether to initiate enforcement action with respect to the compounding of drugs for use in animals. Some of the factors identified in the CPG include considering whether a firm:

- compounds drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drug compounded after receiving prescriptions issued within the confines of a valid veterinary-client-patient relationship;
- compounds drugs for use in animals where an approved new animal drug or approved human drug used, as labeled or in conformity with Title 21, Code of Federal Regulations, Part 530 will, in the available dosage form and concentration, appropriately treat the condition diagnosed;
- compounds finished drugs from human or animal drugs that are not the subject of an approved application, or from bulk drug substances, other than those specifically addressed for regulatory discretion by the FDA, Center for Veterinary Medicine (CVM);
- labels a compounded animal drug with a withdrawal time established by the pharmacist instead of the prescribing veterinarian.

As discussed below, our inspection revealed that your firm engages in activities that fall outside the traditional practice of pharmacy compounding. These activities have resulted in significant violations of the new human and animal drug provisions of the FDCA.

B. Inspectional Findings

Your firm produces domperidone 10mg capsules, and polidocanol 0.25%, 1%, 2%, 3%, and 5% injections for human use. Domperidone and polidocanol are not active ingredients contained in any FDA-approved drug product. FDA does not sanction the use of domperidone and polidocanol in pharmacy compounding and will not exercise its enforcement discretion for drugs produced by your firm, that contain domperidone or polidocanol.

In addition, your firm makes adenosine-5-monophosphate 25 mg/mL, and 100 mg/mL injections for human use. Adenosine-5-monophosphate was removed from the market in 1973 because it was found to be neither safe nor effective. FDA will not exercise enforcement discretion for compounding of drugs containing adenosine-5-monophosphate.

Further, your firm produces finished drug products that are copies of commercially available FDA-approved products or that are essentially copies of commercially available products. These products include:

Isoproterenol 1:5000 injections (human)
Hyaluronidase 150 units/mL injections (human)
Hyalurinodase 500 units/mL (human)
Procaine 2% injections (human)
Methotrexate 25 mg/mL (human)
Isoproterenol 32 picomole/0.2 mL (human)
L-carnitine in 100 mg/ml and 500 mg/mL injections (human)
Enrofloxacin 22.7mg capsules (veterinary)
Chloramphenicol 100mg capsules (veterinary)
Dexamethasone Sodium Phosphate 4 mg/ml injections (veterinary)
Prednisolone 5 mg tablets (veterinary)

We are not aware of any legitimate medical need for the insignificant variations in the formulation of your firm's products from the commercially available products with which they compete. When asked if your firm has documentation of a medical need for the particular variation of the versions of otherwise commercially-available products, your response was that your firm does not.

We also note that batches of these products are produced in excess of actual prescription orders. From January to December 2005, Pharmacy Creations produced the following products:

- [redacted] multi-dose vials of Isoproterenol injections 32 picomoles/0.2ml
- [redacted] multi-dose vials of Hyalurodinase injections 500 u/ml
- [redacted] multi-dose vials of Hyalurodinase injections 150 u/ml
- [redacted] multi-dose vials of Procaine 2% injections
- [redacted] multi-dose vials of L-Carnitine injections 100 mg/ml
- [redacted] multi-dose vials of L-Carnitine injections 500 mg/ml

As explained above, there is no demonstrated medical need for your products that are essentially copies of commercially available products. Given this lack of need, this large volume of products goes well beyond the scope of traditional pharmacy compounding and is instead more representative of a drug manufacturer.

C. Violations of the FDCA

Your firm and the drugs that your firm produces violate the following provisions of the FDCA:

1. Unapproved New Drug Under Section 505 of the FDCA [21 U.S.C. § 355]

The human drug products produced by your firm are unapproved new drugs within the meaning of section 505 of the FDCA [21 U.S.C. § 355] and may not be introduced into interstate commerce without an FDA-approved new drug application.

2. Misbranded Drugs Under Section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)]

Your human and animal drug products are misbranded under section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)] in that their labeling fails to bear adequate directions for use. Further, 21 C.F.R. § 201.115 does not exempt these products from section 502(f)(1) because they are new drugs within the meaning of section 201(p) of the FDCA [21 U.S.C. § 321(p)], or new animal drugs within the meaning of section 201(v) of the FDCA [21 U.S.C. § 321(v)], and they lack approved applications filed pursuant to section 505 or 512 of the FDCA [21 U.S.C. §§ 355 and 360b] and do not otherwise comply with section 505(i) or 512 of the FDCA [21 U.S.C. §§ 355 and 360b].

3. Adulterated Animal Drugs Under Section 501(a)(5) of the FDCA [21 U.S.C. § 351(a)(5)]

The animal drug products produced by your firm are considered new animal drugs within the meaning of section 201(v) [21 U.S.C. § 321(v)] of the FDCA. A new animal drug may not be legally marketed unless it is subject of an approved New Animal Drug Application as required by section 512(a)(1)(A) of the FDCA [21 U.S.C. § 360b(a)(1)(A)]. The animal drugs produced by your firm are unsafe within the meaning of section 512(a) of the FDCA [21 U.S.C. § 360b(a)] because they are new animal drugs but are not the subject of approved New Animal Drug Applications. As such, they are adulterated under section 501(a)(5) of the FDCA [21 U.S.C. § 351(a)(5)]. Sections 512(a)(4) and (5) of the Act [21 U.S.C. §§ 360b(a)(4) and (5)], and their implementing regulations, allow some extra label use of approved animal and human drugs, including compounding from approved animal and human drugs. These provisions, however, apply only to approved drugs and do not permit compounding from bulk active ingredients [see 21 C.F.R. § 530.13(a)].

4. Misbranded Drugs Under Section 502(o) of the FDCA [21 U.S.C. § 352(o)]

The human and animal drug products produced by your firm are misbranded under section 502(o) of the FDCA [21 U.S.C. § 352(o)] in that they are manufactured in an

establishment not duly registered under section 510 of the FDCA [21 U.S.C. § 360], and the drugs have not been listed as required by section 510(j) of the FDCA [21 U.S.C. § 360(j)]. Your facility is not exempt from registration and drug listing under section 510(g) of the FDCA [21 U.S.C. § 360(g)] or 21 C.F.R. § 207.10.

5. Adulterated Drugs Under section 501(a)(2)(B) of the FDCA [21 U.S.C. § 351(a)(2)(B)

Your drug products are adulterated under section 501(a)(2)(B) of the FDCA [21 U.S.C. § 351(a)(1)(B)] because the controls and procedures used in their manufacture, processing, packing, and holding do not conform to current good manufacturing practice regulations, 21 CFR Parts 210 and 211. Deviations from these regulations include, but are not limited to the following:

a. Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not followed and do not include validation of the sterilization process [21 CFR § 211.113(b)]. Specifically:

i. The oven used to sterilize vials of suspension products and the dry heat oven used to sterilize vials of injectable hormone products in oils have not been validated for their intended purpose. The efficacy of the sterilization cycles has not been demonstrated using actual loads.

ii. Environmental monitoring is not performed in the isolator during aseptic filling operations. The monitoring is performed only once every six months and with settling plates that are incubated at a single temperature that will not promote the growth of all recovered contaminating organisms. No positive or negative controls are used. No smoke studies or media fills have been performed to demonstrate the efficacy of the isolator.

iii. There are no written procedures for the use and operation of the isolator. In addition, there are no written procedures for the isolator's maintenance, cleaning, and sanitization, as required by 21 CFR § 211.67(b).

b. Failure to establish laboratory controls, including scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR § 211.160(b)]. In particular, specifications for acceptable levels of endotoxin have not been established for several of your sterile injectable drug products.

c. Failure to test each batch of drug product for satisfactory conformance to the final specifications for the drug product, prior to release [21 CFR § 211.165(a)]. Specifically, no testing is performed on batches of non-sterile drug products.

d. Failure to establish adequate written procedures for production and process control designed to assure that drug products have the identity, strength, quality, and purity that they purport or are represented to possess [21 CFR § 211.100(a)]. Specifically, your firm lacks written procedures for sterile compounding, environmental monitoring, aseptic filling, and in-house sterility testing that are specific to your operations.

e. Failure to subject each lot of drug product component that is liable to microbiological contamination that is objectionable in view of its intended use to microbiological tests before use [21 CFR § 211.84(d)(6)]. Specifically, no bioburden testing is performed on the raw materials or bulk solutions used to make sterile injectable products, prior to sterilization.

f. Failure to establish separate or defined areas or other control systems necessary to prevent contamination and mix-ups in the course of drug manufacturing and processing operations [21 CFR § 211.42(c)(5)]. Specifically, employees of your firm were seen manufacturing different products in close proximity to each other on the same laboratory table.

g. Failure to prepare batch production and control records for each batch of drug product, including complete information on the production and control of each batch [21 CFR §§ 211.188(b)(1), (3), (10), and (11)]. Specifically:

i. Some compounding sheets lack dates of manufacture.

ii. Some compounding sheets lack specific identification of each batch of components or in-process materials used.

iii. Compounding sheets for sterile injectable products lack records of any samples collected for the contract laboratory performed tests for potency, sterility, and endotoxin levels.

iv. Some compounding sheets lack identification of the persons performing and directly supervising or checking each significant step in the manufacturing process.

We have received your written response dated February 9, 2006, submitted by your attorney. Your response is not satisfactory in that you intend to continue producing copies of commercially available human and animal products without documenting the medical need for these products. The letter also stated that Pharmacy Creations does not prepare duplicates of any commercially available products. However, we do not consider the availability of different size vials a meaningful distinction between your products and commercially available products. Further, your products appear to have strengths that can be obtained through the use of commercially available products. Your response does not address any specific corrections that you will make at your firm.

In addition, the corrective actions outlined in the response pertaining to record keeping and sterilization are inadequate in that they fail to address some of the problems discussed during the inspection, lack detail, and are not supported by any documentation. For example, with respect to the SOPs, the tightening of controls for documentation and improvements to sterilization procedures, the response fails to describe any specific corrective actions. Regarding the response's discussion of the barrier isolator, you do not make clear what is meant by the term "FDA approved" in this context. Also, the response fails to address other issues raised during the inspection, such as your firm's environmental monitoring program.

We also note that your firm produces two benzocaine-lidocaine-tetracaine (BLT) creams: benzocaine 20%, lidocaine 10%, tetracaine 4% and benzocaine 20%, lidocaine 6%, tetracaine 4% for human use. Please be aware that the agency is concerned with the public health risks associated with the sale of BLT creams. There have been at least

two non-fatal reactions and two deaths attributed to the use of compounded topical creams containing high doses of local anesthetics. Local anesthetics, like BLT creams, may be toxic at high dosages and this toxicity can be additive. Further, there is a narrow difference between the optimal therapeutic dose of these products and their associated toxicity, i.e., they have a low therapeutic index.

The above violations are not intended to be an all-inclusive list of deficiencies at your facility and they may not be limited to the above-cited drug products. It is your responsibility to ensure that all requirements of the FDCA and the associated regulations are being met. Federal agencies are routinely advised of the issuance of warning letters so that they may take this information into account when considering the award of government contracts.

You should take prompt action to correct these violations. Failure to do so may result in additional regulatory action without further notice, including seizure of your products and/or injunction.

Please notify this office in writing within 15 working days of receipt of this letter of the actions that you have taken to correct the noted violations, including an explanation of the steps taken to prevent their recurrence. 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.

Please direct your response to Sarah A. Della Fave, Compliance Officer, U.S. Food and Drug Administration, New Jersey District, 10 Waterview Boulevard, 3rd Floor, Parsippany, New Jersey 07054.

Sincerely,

Douglas I. Ellsworth
District Director
New Jersey District