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DEPARTMENT OF HEALTH AND HUMAN SERVICE

Public Health Service

Food and Drug Administration
Kansas City District
Southwest Region
11630 West 80th Street
Lenexa, Kansas 66214-3340

Telephone: (913) 752-2100

January 14, 2008

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER
Ref. KAN 2008-03

Paul M. Hueseman, President
Bellevue Pharmacy Solutions
1034 S. Brentwood Blvd.
St. Louis, MO 63117

Dear Mr. Hueseman:

Based on your firm's Website, www.bpharmacysolutions.com, and mailed advertisements to physicians, it has come to our attention that your firm compounds and distributes drugs, including hyaluronidase, progesterone, diphenhydramine, dimenhydrinate, folic acid, pyridoxine, thiamine, and EDTA (edetate disodium). It appears that your firm also compounds products containing polidocanol, cantharidin, estriol, and domperidone, which are not components of any FDA-approved drug. If your firm is compounding any of these products, it is in violation 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 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 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. Compounding Copies and Near Copies of FDA-Approved, Commercially Available Drugs

Your firm's Website, www.bpharmacysolutions.com, indicates that you compound drugs including the following products:

[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.

[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.

- Hyaluronidase 150 units/ml injections
- Progesterone 100 mg/200 mg capsules
- Diphenhydramine 50 mg/ml injections
- Dimenhydrinate 50 mg/ml injections
- Folic Acid 5 mg/ml injections
- Pyridoxine Hydrochloride 100 mg/ml injections
- Thiamine Hydrochloride (B-1) 100 mg/ml injections
- Edetate Disodium (EDTA) 150 mg/ml injections

These products are copies or essentially copies of FDA-approved drugs and appear to be compounded without a patient-specific medical need, as determined by a licensed healthcare provider, for their variation from the FDA-approved, commercially-available drugs with which they compete. We will not exercise enforcement discretion toward your firm's continued compounding of these drugs.

C. Products Using Active Ingredients that Are Not Components of FDA-Approved Drug Products

Your firm's promotional materials offer compounding services for products that are not components of FDA-approved drugs. These promotional materials indicate that your firm produces polidocanol 5% injection, cantharidin, and hormone therapy drugs containing estriol.

FDA is concerned with the public health risks associated with the compounding of polidocanol. Known adverse events include deep venous thromboses, necrosis, and ulceration at the treated site with polidocanol. Reversible cardiac arrest after polidocanol sclerotherapy has been reported.

Further, cantharidin and estriol are not components of an FDA-approved drug, and your firm compounds these products without FDA-sanctioned INDs.

We also have reason to believe that your firm may be compounding domperidone. FDA is concerned with the public health risks associated with the compounding of domperidone. There have been several published reports and case studies of cardiac arrhythmias, cardiac arrest and sudden death in patients receiving an intravenous form of domperidone that has been withdrawn from the market in several countries. FDA has become aware of the use of domperidone by

lactating women to increase breast milk production because of its effect on prolactin levels. While domperidone is approved in several other countries for the treatment of gastric stasis and gastroparesis, domperidone is not approved in any country for enhancing breast milk production in lactating women. In several countries where the oral form of domperidone continues to be marketed, labels for the product note that domperidone is excreted in the breast milk of lactating women and recommend that women taking domperidone avoid breast-feeding. Because of this, FDA recommends that breastfeeding women not use domperidone to increase milk production.

Polidocanol, cantharidin, estriol and domperidone are not active ingredients contained in any FDA-approved drug. FDA does not sanction their use in pharmacy compounding and will not exercise enforcement discretion with respect to products that contain these ingredients.

D. Violations of the FDCA

Unapproved New Drugs

The aforementioned products compounded by your firm are drugs within the meaning of section 201(g) of the FDCA [21 U.S.C. § 321(g)]. They are also new drugs under section 201(p) of the FDCA [21 U.S.C. § 321(p)] that may not be introduced or delivered for introduction into interstate commerce under section 505 of the FDCA [21 U.S.C. § 355] because no approval of an application filed pursuant to section 505(b) or (j) of the FDCA [21 U.S.C. §§ 355(b), (j)] is in effect for them. Their introduction or delivery for introduction into interstate commerce violates section 301(d) of the FDCA [21 U.S.C. § 331(d)].

In addition, these drugs are misbranded under section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)] because their labeling fails to bear adequate directions for their use, and they are not exempt from this requirement under 21 CFR § 201.115, and do not otherwise comply with section 505(i) of the FDCA [21 U.S.C. § 355(i)]. Section 301(a) of the FDCA [21 U.S.C. § 331(a)] prohibits the introduction or delivery for introduction into interstate commerce of any misbranded drug, and section 301(k) of the FDCA [21 U.S.C. § 331(k)] prohibits any act with respect to a drug if the act is done while the drug is held for sale after shipment in interstate commerce and results in the drug being misbranded.

The issues and violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to assure that your firm complies with all requirements of federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the time within which you will complete the correction. Please direct your response to Nadine Nanko Johnson, Compliance Officer, U.S. Food and Drug Administration, at the address listed above.

Sincerely,

for/ John W. Thorsky
District Director
Kansas City District