S7040C

DEPARTMENT OF HEALTH & HUMAN SERVICE

Public Health Service
Food and Drug Administratio
Los Angeles District

19701 Fairchild
Irvine, California 92612-2506
Telephone (949) 608-2900
Fax (949) 608-4401

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

November 12, 2008 WL 04-09

Charles T. Bonner, R.Ph., President
Steven's Pharmacy
1525 Mesa Verde Drive
Costa Mesa, CA 92626-5221

Dear Mr. Bonner:

On June 23-25, 2008, a U.S. Food and Drug Administration (FDA) investigator conducted an inspection of your facility, located at 1525 Mesa Verde Drive, Costa Mesa, California. 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

The FDCA establishes agency jurisdiction over "new drugs," including compounded drugs. Compounded drugs fit within the FDCA's definition of "new drug": "[a]ny drug (except a new animal drug . . .) [that] is not generally recognized . . . as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof." 21 U.S.C. § 321(p)(1). *See also 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 Medical Ctr. Pharm. v. Mukasey,* 2008 U.S. App. LEXIS 15276, No. 06-51583, (5th Cir. July 18, 2008) ("compounded drugs are not exempt from the FDCA's 'new drug' definition, § 321(p), nor are they uniformly exempt from the FDCA's 'new drug' requirements, §§ 351(a)(2)(B), 352(f)(1), 355"); *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) ("The FDCA contains provisions with explicit exemptions [from] the new drug . . . provisions. Neither pharmacies nor compounded drugs are expressly exempted."), *aff'd, Wedgewood Village Pharmacy v. United States,* 421 F.3d 263, 269 (3d Cir. 2005). The drugs that pharmacists compound are not FDA-approved and lack an FDA finding of safety and efficacy. Because compounded drugs are "new drugs" under the FDCA that are unapproved, the statute generally prohibits their introduction into interstate commerce.

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. As a matter of agency discretion, FDA has historically not taken enforcement action against traditional compounding in recognition of the benefit that it affords patients when FDA-approved, commercially available drugs are inadequate or unavailable.

In 1997, Congress enacted, as part of the Food and Drug Administration Modernization Act of 1997 (FDAMA), a provision that related to pharmacy compounding, codified in section 503A of the FDCA (21 U.S.C. § 353a). In 2001, the Ninth Circuit Court of Appeals declared this section invalid because it included unconstitutional restrictions on commercial speech and those restrictions could not be severed from the rest of section 503A. *Western States Medical Center v. Shalala,* 238 F.3d 1090 (9th Cir. 2001). The Supreme Court affirmed the Ninth Circuit ruling that the advertising restrictions violated the First Amendment, but it did not consider whether these restrictions could be severed from the rest of section 503A. *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002). In 2008, the Fifth Circuit Court of Appeals held that the restrictions on commercial speech could be severed from the rest of 503A and that the remainder of 503A is valid and in force. *Medical Ctr. Pharm. v. Mukasey,* 2008 U.S. App. LEXIS 15276. Thus, the decisions of the Fifth and Ninth Circuits directly conflict on whether the non-advertising provisions of section 503A are valid and in effect.

FDA has determined at this time that it will apply the non-advertising provisions of section 503A to entities covered by this provision that are located within the jurisdiction of the Fifth Circuit (i.e., Texas, Louisiana, and Mississippi) as well as to the plaintiffs that brought the *Medical Ctr. Pharm.* case. Elsewhere, FDA will continue to apply the enforcement policy 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)). The CPG identifies a non-exhaustive list of factors that the Agency considers in deciding whether to initiate an enforcement action with respect to compounding. These factors include, among other things, compounding drugs in anticipation of receiving prescriptions (except in very limited amounts), using active pharmaceutical ingredients that are not components of FDA-approved drugs, compounding for third parties who resell to individual patients, and compounding drugs that are essentially copies of commercially available drugs.

B. Factual Background

Your firm purports to be a compounding pharmacy, but our investigation found that your operation exceeds the practices associated with traditional extemporaneous compounding and is more akin to that of a drug manufacturer. Your firm manufactures large volumes of drugs including, but not limited to, (b) (4) standardized topical anesthetic drugs[1] ("Profound

[1]Please be advised that the FDA issued a public health alert regarding the risks associated with the use of compounded combinations of high concentration topical anesthetic drugs (http://www.fda.gov/bbs/topics/NEWS/2006/NEW01516.html).

Gel," and "Profound Gel Light"), (b) (4) products in anticipation of receiving prescriptions.

From (b) (4) to (b) (4), your firm produced: over (b) (4) (b) (4) with batch sizes ranging from (b) (4); and over (b) (4) of the topical anesthetic drugs, "Profound Gel" ((b) (4) prilocaine, (b) (4) lidocaine, and (b) tetracaine) and "Profound Gel Light" (b) prilocaine, (b) lidocaine, and (b) tetracaine), in batch sizes ranging from (b) (4) and dispensed in package sizes of (b) (4) (b) (4) Compounding records for other topical drug products, such as your (b) (4) compounded between (b) (4) and (b) (4) show that your firm produced at least (b) (4) of this product in batch sizes up to (b) (4). Additionally, there were over (b) (4) dosage form units of (b) (4) produced during the same time interval in strengths of (b) (4) in batch sizes ranging from (b) (4) units per batch. The production of these volumes of standardized prescription drug products is inconsistent with traditional extemporaneous compounding, which involves compounding a medication based on a specific medical need of an individually-identified patient. For commonly ordered compounded prescription drugs, your firm produces drugs in anticipation of receiving prescriptions. Such anticipatory inventory of topical anesthetic drugs was noted during the recent FDA inspection of your firm.

In addition to producing drug products in anticipation of receiving prescriptions, your firm produces large volumes of compounded products, including copies of FDA-approved commercially available products. Examples include (b) (4) and (b) (4). Other products compounded by your firm are essentially copies of FDA-approved commercially available products, including alternate oral dosage forms, such as (b) (4) These essential copies appear to be produced without a documented patient-specific medical need, as determined by a licensed healthcare provider, for these versions of otherwise commercially available drugs.

During the inspection, you stated that approximately (b) (4) of all finished drug products are distributed outside of California. Your firm is engaged in the commercial-level distribution of standardized drug products, as you provide preprinted order forms and promotional material to practitioners and obtain orders from dentists that contain a list of drugs to be compounded by your firm, including for your topical anesthetic prescription drug products. Moreover, the use of the terms "Profound Gel" and "Profound Gel Light" implies the standardization of a compounded drug product rather than extemporaneous compounding for individually-identified patients. This practice is outside the traditional scope of pharmacy compounding and more akin to that of a drug manufacturer.

FDA is seriously concerned about the public health risks and safety issues related to the compounding and sale of (b) (4) The Drug Addiction Treatment Act of 2000 (DATA) was passed into law on October 17, 2000, allowing qualified practitioners who want to treat narcotic dependent patients to administer, dispense, and prescribe schedule III-V narcotic substances approved by FDA specifically for the use in maintenance and detoxification treatment. Currently, the only (b) (4) -based products that FDA has approved for detoxification treatment are (b) (4) in their respective strengths. No other

medications, including compounded (b) (4) products, are eligible for (b) (4) treatment under DATA. At the close of the last inspection, you were provided a letter from the Drug Enforcement Agency (DEA) stating that practitioners can only prescribe (b) (4) from FDA-approved products and not compounded products.

Similarly, FDA is concerned about the serious public health risks related to compounded topical anesthetic products. Topically applied local anesthetics have been associated with dose-related local and systemic toxicity which can be serious. Exposure to high concentrations of local anesthetics, like those in your firm's compounded topical anesthetic products, can cause grave reactions, including seizures and irregular heartbeats. Your firm's compounded topical anesthetic products contain high doses of local anesthetics including lidocaine, tetracaine, benzocaine, and prilocaine. These high concentrations of prilocaine (b) (4) and lidocaine (b) (4) for example, are not approved for topical use. When different anesthetics are combined into one product, each anesthetic's potential for harm is increased. This potential harm may also increase if the product is left on the body for long periods of time or applied to broad areas of the body, particularly if an area is then covered by a bandage, plastic, or other dressing. The risk of harm is even greater in small children, patients with pre-existing heart disease, and patients with severe liver disease. To illustrate this risk, prilocaine and other local anesthetics have been associated with serious cases of systemic toxicity, including methemoglobinemia, particularly when administered to pediatric patients.

Furthermore, the pharmacy information sheet for your firm's compounded topical anesthetics does not include indications for the products. Precautions to avoid systemic toxicity associated with the local anesthetics were inadequately represented in the information sheet. For example, risks such as methemoglobinemia, otic toxicity, and interference with anti-arrhythmic and antibiotics were not described. There were no dosing adjustments for geriatric patients, pediatric patients, or patients with a deficiency of circulating esterases. It is unclear where on the body the product is to be used, which may result in application to sites where there is an increased risk of local irritation or systemic absorption. The information sheet contends that there are no reports of fetal malformations and that maternal exposure is safe for nursing infants. The label does not contain adequate information to support these claims and may be misleading. There are also no data provided to support the safety and efficacy of a combination of topical prilocaine, lidocaine and tetracaine for any indication.

In addition to the lack of adequate information on product safety and indication, the pharmacy information sheet for Profound Gel contains limited dosing information. The dose recommended in the information sheet is a "small amount." However, the unit dosing is quantified only in terms of the dose weight, a measurement that is unlikely to be available in practice. Dosing of approved topical anesthetic products is typically described by the surface area of the skin to be covered and the thickness of the application or the length of the expressed product from a tube through a fixed orifice as a volume measurement. Therefore, unclear dosing recommendations for the compounded products increase the potential for systemic toxicity resulting from an overdose of local anesthetic. The information sheet further states that symptoms of overdosage originate in the central nervous system and in the cardiovascular system, but does not indicate what symptoms may occur or how they are to be managed safely. The information sheet also does not detail clinical pharmacology of the active ingredients. In essence, the product information sheet lacks the detail needed to use the product safely.

Your firm also compounds (b) (4) containing (b) (4), which is not a component of an FDA-approved drug and has not been demonstrated under FDA standards to be safe and effective for any use. Pharmacies may not compound drugs containing (b) (4) unless a doctor prescribing the drug obtains a valid investigational new drug application (IND). INDs are important to patient safety. Physicians wishing to treat their patients with drugs containing (b) (4) can learn about the IND process at http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm. Your firm produces these products without an FDA-approved new drug application (NDA) or an FDA-sanctioned investigational new drug (IND) application, in violation of section 505 of the FDCA (21 USC § 355). FDA does not sanction the use of (b) (4) in pharmacy compounding and will not exercise enforcement discretion with respect to products that contain this ingredient.

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 aforementioned 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 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)].Your firm's topical anesthetic drug products, including Profound Gel and Profound Gel Light, are misbranded under Section 502(a) of the FDCA [21 U.S.C. § 352(a)], as further defined in Section 201(n), 21 U.S.C. § 321(n), because their labels fail to reveal adequate information to support the safe use of the products, contain limited dosing information, and contain no clear indication and intended route of administration, facts material with respect to adverse health consequences that may result from the use of the articles by individuals with underlying medical conditions or those otherwise at risk for adverse drug side effects.

D. Conclusion

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.

Your written reply should be addressed to:

John Stamp
Compliance Officer
Food and Drug Administration
19701 Fairchild
Irvine, CA 92612-2506

If you have any questions regarding this letter, please contact Mr. John Stamp, Compliance Officer at (949) 608-4409.

Sincerely,

Alonza E. Cruse
District Director
Los Angeles District