W-L-File

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration
New England District

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October 31, 2008

Mr. Barry J. Cadden, Director and Pharmacy Owner
New England Compounding Center
697 Waverly St.
Framingham, MA 01702

Dear Mr. Cadden:

This letter replies to your January 5, 2007 response to an FDA Warning Letter issued to your firm on December 4, 2006. We acknowledge and apologize for the significant delay in this correspondence.

Your letter asserts that the unapproved drug and misbranding charges in the Warning Letter do not apply because of the decision in *Medical Center Pharmacy v. Gonzales*, 451 F. Supp. 2d 854 (W.D. Tex. 2006). You also state that your firm engages in "the kind of activity that the *Medical Center Pharmacy* court determined does not result in the introduction of new drugs into interstate commerce."

As stated in the Warning Letter, 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 Professionals & 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.

As to your argument based on *Medical Center Pharmacy v. Gonzales*, 451 F. Supp. 2d 854 (W.D. Tex. 2006), on July 18, 2008, the United States Court of Appeals for the Fifth Circuit issued a ruling in the case on appeal. *Medical Center Pharmacy v. Mukasey*, 536 F. 3d 383 (5th Cir. 2008). The Fifth Circuit rejected the finding by the United States District Court for the Western District of Texas that compounded drugs are exempt from the definition of "new drugs" in the FDCA. The Fifth Circuit concluded instead that compounded drugs are "new drugs." The court also ruled on the severability of advertising prohibitions in section 503A of the FDCA, which were found unconstitutional in a prior Supreme Court decision, *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002).[1] The Fifth Circuit held that the restrictions on commercial speech in section 503A of the FDCA could be severed from the rest of 503A and that the remainder of 503A is valid and in force.

The Fifth Circuit's severability ruling conflicts with an earlier decision by the United States Court of Appeals for the Ninth Circuit, which held that the unconstitutional parts of section 503A are not severable and that all of section 503A is therefore void. *Western States Medical Center v. Shalala*, 238 F.3d 1090 (9th Cir. 2001). 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 Center Pharmacy* case. Elsewhere, including in Massachusetts, the agency will continue to follow the enforcement approach reflected in the 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)).

Your letter states that your firm does not introduce unapproved drugs into interstate commerce and does not need approved NDAs before dispensing its compounded medications. We disagree. As explained above, FDA regards compounded drugs as new drugs that require agency approval before they are introduced into interstate commerce. Your firm's compounded products lack this approval and therefore violate the FDCA.

Also as explained above, while compounded drugs violate the FDCA, FDA generally exercises enforcement discretion when they are the result of traditional pharmacy compounding. This discretion is contingent on factors such as the preparation of patient-specific drugs that meet medical needs for which FDA-approved drugs are unavailable.

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[1] 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).

You state that you compound topical anesthetic formulas solely in accordance with formulas determined by the prescribing physicians. We acknowledge that you will require physicians to specify the chemical formulation on each patient-specific prescription for compounded topical anesthetic drugs. You also asked us to advise you whether using the term "triple anesthetic cream" to describe your compounded drug product is problematic. We find that use of this term implies the standardization of a compounded drug product rather than extemporaneous compounding for individually identified patients.

In the Warning Letter, FDA also expressed concern that you were generating sales for the "triple anesthetic cream" by providing physicians with "courtesy prescriptions" (*i.e.*, free samples) of compounded drugs, without valid prescriptions that respond to patient-specific medical need, which would indicate the distribution by your firm of a standardized drug product. The development of a standardized drug product is inconsistent with the traditional practice of pharmacy compounding where pharmacists extemporaneously compound drugs upon receipt of valid prescriptions. In your response you assert that these "courtesy samples" are dispensed "only upon receipt of a valid prescription from a licensed practitioner to meet the unique medical needs of a particular patient" and that these are not samples as that term is defined in the Prescription Drug Marketing Act (PDMA). The Warning Letter did not allege that your practice violates the PDMA, and FDA does not take a position on this issue at this time. Nevertheless, we acknowledge your response that you provide a small amount of medication free of charge only upon receipt of a valid prescription. We will evaluate in a future inspection your current practices and any changes that you make to those practices and assess whether, despite these practices and changes, you produce standardized topical anesthetic products. We will not exercise enforcement discretion toward such products.

Please note that your letter does not alleviate our concern about the health risks associated with the topical anesthetics compounded by your firm. You state that "Virtually all drugs, including manufactured drugs, pose serious health risks if they are misused by physicians or patients." But the drugs compounded by your firm may be dangerous even if used as directed because they are extremely potent in comparison to FDA-approved topical anesthetic drugs. As noted in the Warning Letter, these risks are exacerbated if the safety-related information that accompanies these products is deficient.

We acknowledge that you have stated that you no longer dispense prescriptions for compounded products containing trypan blue or 20% aminolevulinic acid solution.

With regard to the repackaging of Avastin, we acknowledge your assertion that you repackage the product only upon receipt of a valid prescription from a licensed practitioner for an individual patient and your argument that this repackaging constitutes

the practice of pharmacy. However, each step in the manufacture and processing of a new drug, including packaging, must be approved by FDA, whether carried out by the original manufacturer or, in most cases, by a repackager. Pharmacists are not exempt from this requirement; however, FDA's Compliance Policy Guide on repackaging (Compliance Policy Guide Sec. 446.100, Regulatory Action Regarding Approved New Drugs and Antibiotic Drug Products Subjected to Additional Processing or other Manipulations) provides that the agency will exercise enforcement discretion toward pharmacists who repackage approved drugs within the practice of pharmacy for use consistent with the drug's approved labeling. Your repackaging is not consistent with Avastin's approved labeling, where you repackage the drug from vials into syringes, and where the labeled precautions include "discard any unused portion left in a vial...."

FDA is concerned about the manipulation of sterile products when a sterile container is opened or otherwise entered to conduct manipulations. The moment a sterile container is opened and manipulated, a quality standard (sterility) is destroyed and previous studies supporting the standard(s) are compromised and are no longer valid. We are especially concerned with the potential microbial contamination associated with splitting Avastin—a single-use, preservative-free vial—into multiple doses. When used intravitreally, microbes could cause endophthalmitis, which has a high probability for significant vision loss. The absence of controls over storage, and delays before use and after repackaging, only exacerbate these concerns.

As stated in the Warning Letter, your repackaging is not consistent with Avastin's approved labeling; therefore, for the reasons stated in the warning letter, we believe that your firm is distributing an unapproved new drug in violation of section 505 of the FDCA and a misbranded drug in violation of section 502(f)(1) of the FDCA.

Finally, we acknowledge your concern about the time between our last inspection of your pharmacy and the issuance of the Warning Letter. We agree that the length of intervening period was unusual. This in no way diminishes our serious concerns about your firm's operation.

Your firm must promptly correct the violations noted in the December 4, 2006, Warning Letter, and establish procedures to assure that such violations do not recur. Its failure to do so may result in enforcement action, including seizure of the firm's products and/or an injunction against the firm and its principals.

In a future inspection, we will confirm the commitments that you made in your response. We also will verify that your firm's compounding practices are consistent with the policy articulated in the CPG, and that your firm's operation is not otherwise at odds with the conditions under which the agency exercises enforcement discretion towards pharmacy compounding.

Please direct any questions you have to Bruce Ota, Compliance Officer. U.S. Food and Drug Administration, New England District Office, One Montvale Ave., 4th Floor, Stoneham, MA 02180.

Sincerely,

Bruce R. Ota
Compliance Officer
New England District Office

NWE: BRO/MSS

cc: R, CF, BRO, WL File