



February 1, 2008

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner
Food and Drug Administration
Parklawn Building
5600 Fishers Lane
Rockville, MD 20857

RE: January 9, 2008 FDA Action against Compounding Pharmacy Operators

Dear Commissioner von Eschenbach:

The American Pharmacists Association (APhA), the International Academy of Compounding Pharmacists (IACP), the National Community Pharmacists Association (NCPA), the National Alliance of State Pharmacy Associations (NASPA), and the American College of Apothecaries (ACA) are writing in response to the Food and Drug Administration's (FDA) recent action against seven compounding pharmacy operators. Combined, these organizations represent more than 125,000 pharmacists and others interested in advancing the profession, including 23,000 community-based pharmacies and the 50 state pharmacy associations.

We appreciate the Agency's reassertion that traditional pharmacy compounding is an important component of our health care system. It allows a pharmacist to use their medication expertise to create a medication tailored to an individual patient's needs. It is in the profession's best interest, therefore, to ensure that this core element of its practice is not only retained but also done appropriately. Consequently, we support the Agency's action to address what has been described as false and misleading marketing of bio-identical hormone replacement therapy (BHRT) products. While we do not take a position on any specific drug products, we agree that marketing BHRT as equally safe and effective as a commercially manufactured product or as a product that could be used to treat cancer, Alzheimer's or another disease is inappropriate unless science can support such claims.

However, we do not agree with the Agency's claims that the compounded products in question violate sections of the Federal Food, Drug and Cosmetic Act (FDCA). Furthermore, we do not agree with the Agency's action regarding the use of estriol as an ingredient in pharmacy compounding.

Do the New Drug Provisions of the FDCA Apply to Compounded Products?

The new drug provisions of the FDCA were created to regulate drug manufacturing, marketing, and distribution. The Act was not aimed at regulating compounding pharmacies or pharmacy practice. For nearly 50 years after the passage of the Act, FDA did not seek to regulate compounding pharmacists, but left this regulation to the States¹, where boards of pharmacy have the authority and responsibility to regulate traditional pharmacy compounding.

The Agency's enforcement activity related to compounded products changed in 1992 when it released its compounding Compliance Policy Guide (CPG), which claimed that compounded drugs were subject to certain provisions of the FDCA:

“It should be noted, however, that while retail pharmacies that meet the statutory requirements of the Federal Food, Drug, and Cosmetic Act (Act), they are not the subject of any general exemption from the new drug, adulteration, or misbranding provisions of the Act.”²

In 1997, Congress passed Food and Drug Administration Modernization Act (FDAMA) to clearly delineate between pharmacy compounding and manufacturing. In doing so, the Act exempted traditionally compounded products from certain requirements that apply to manufactured products, including those requirements for which the operators in question are cited.

Once enacted, FDAMA's compounding-related sections were the focus of lawsuits questioning the constitutionality of FDAMA's advertising restrictions and whether compounded drugs should be exempted from FDCA requirements for new drugs. While these questions remain in the courts, several rulings are relevant to this discussion. The U.S. District Court, for the Western District of Texas ruled in 2006 that compounded drugs do not fall under the definition of a new drug³. Additionally, the Supreme Court ruled in *Western States* that regulating compounding drugs as new drugs would be impractical.⁴ And further rulings are pending.

Given the Congressional intent of FDAMA to exempt compounded drugs from “new drug” requirements and the Court's support for that action, we strongly oppose the Agency's decision to take such enforcement action against compounding pharmacies and question the Agency's authority to do so. It is also inappropriate for the Agency to take enforcement action on issues that are the subject of pending litigation.

Relevance of CPG

In addition to the general question of whether the FDA has the authority to regulate compounding under the new drug provisions of the Act, we question the Agency's use of its CPG 460.200. In the

¹ *Thompson v. Western States Medical Center*, 122 S.Ct. 1497, 1501 (2002).

² Food and Drug Administration. “Background.” *Compliance Policy Guides: Chapter 32 – Drugs General (7132.16)*. March 16, 1992. Pg. 1.

³ *Medical Center v. Gonzales*, 451 F.Supp2d 854 (2006).

⁴ *Thompson* at 1505

CPG, the Agency explains that the Supreme Court's invalidation of section 503A of the FDCA compelled the Agency to provide guidance to the compounding industry on what factors the Agency will consider in exercising its enforcement of pharmacy compounding. Furthermore, traditional pharmacy compounding is not the subject of the guidance. Rather, according to FDA, the CPG will be used to take enforcement action against pharmacy operators who are compounding in a manner that reflects manufacturing.

Over pharmacy's objections, the CPG is substantially more restrictive than FDAMA and attempts to assert the FDA's authority to take enforcement actions related to all compounding. After its June 2002 release, several of our organizations expressed significant concerns with the CPG, including the Agency's decision to revert to its pre-FDAMA (more restrictive) position on pharmacy compounding and the factors identified to distinguish between traditional pharmacy compounding and manufacturing. For today's purposes, our comments focus on the purpose of the CPG and Factor 3.

Purpose of the CPG

The CPG contains nine factors that the FDA will consider when determining whether to initiate enforcement action. The factors are intended to help the Agency distinguish compounding from manufacturing. We are concerned that several of the factors do not appear to address manufacturing, but rather address safety issues and good compounding practices.

In its 2002 comments, we expressed our concerns with using factors related to good compounding practices to determine if an entity is acting as a manufacturer and with FDA setting or measuring compounding safety standards. This authority continues to rest with the state boards of pharmacy, and other standard setting organizations such as the U.S. Pharmacopoeia (USP) and the Pharmacy Compounding Accreditation Board (PCAB).

The warning letters highlight the inappropriate use of the CPG, which is being used to regulate the practice of pharmacy rather than as a tool to help FDA determine when to take action against an entity that is manufacturing under the guise of compounding. There is nothing to suggest in the letters sent by the Agency to the seven pharmacy operators that they were manufacturing. We strongly oppose the Agency using the CPG for reasons that do not reflect its purpose. It is completely inappropriate and not within the scope of the CPG.

Furthermore, the CPG does not have the force of law or regulation. The courts and law agree. In 1995, the United States Court of Appeals for the Fifth Circuit held that the 1992 CPG was not a substantive rule.⁵ And in its *Western States* ruling, the Supreme Court found that the CPG is not binding and merely reflects the Agency's current thinking on what might be subject to an enforcement action.

The Restrictions of Factor 3

We do not agree that the CPG should be used to regulate best compounding practices and Factor 3 demonstrates the challenges with using the CPG in this manner. The warning letters cite the pharmacy operators for not complying with the CPG's Factor 3, which states:

⁵ *Professionals and Patients for Customize Care v. Shalala*, 56 F.3d 592 (1995)

*Factor 3: Compounding finished drugs from bulk active ingredients that are not components of FDA approved drugs without an FDA sanctioned investigational new drug application (IND) in accordance with 21 U.S.C. § 355(i) and 21 CFR 312.*⁶

The Agency states that the pharmacy operators are compounding using the ingredient estriol, which is not a component of an FDA-approved drug product. Use of estriol is consistent with United States Pharmacopeia (USP) — recognized as an official compendium in FDCA(21 U.S.C. 321) — standards for pharmacy compounding. Use of estriol is also consistent with the standards of the Pharmacy Compounding Accreditation Board (PCAB). Finally, use of estriol is consistent with FDAMA, which listed three sources of bulk drug ingredients that could be used in compounding:

1. drug substances that are components of drugs approved by the Secretary,
2. drug substances that comply with the standards of an applicable U.S. Pharmacopoeia or National Formulary monograph (if a monograph exists), and/or
3. drug substances that appear on a list developed by the Secretary.⁷

As we indicated above, the current CPG is more restrictive than FDAMA, and therefore Congressional intent. The current CPG is designed to reduce the number of potential sources for bulk drug products from three to one, allowing only the use of bulk drug products that are components of FDA approved drugs.

The CPG fails to address the use of drugs that have been on the market since before the development of the FDA process in 1938. For example, while not technically considered FDA-approved, acetaminophen, aspirin, phenobarbital and chloral hydrate are commonly compounded for specific needs based upon a physician order. Limiting bulk drug ingredients to drugs that are components of FDA-approved drug products greatly limits the number of ingredients that can be used to prepare compounded products and reduces pharmacists' and physicians' ability to provide their patients with medications tailored to their individual needs. Again, these limits are inconsistent with Congressional intent when they enacted FDAMA; nor do they reflect PCAB's or USP standards — all three of which allow for compounding using ingredients that meet United States Pharmacopeia/National Formulary grade standards — such as estriol.

Our concerns with this and other factors of the CPG were expressed when the new CPG was released in May 2002. At that time, we recommended that the Agency eliminate this factor from the CPG or reinstate the three sources of bulk drug ingredients. Many state board of pharmacy regulations already list acceptable bulk substances. The Agency could easily revise the guidance (not a regulation) to reinstate this list and acknowledge that bulk drug substances with U.S Pharmacopeia (USP) or National Formulary (NF) monographs — such as estriol — are suitable for compounding.

Conclusion

The FDA has been empowered by Congress to regulate the *manufacturing* of pharmaceuticals; the regulation of pharmacy practice—and of compounding—remains a state function. Historically, state boards of pharmacy have regulated pharmacists and pharmacy practice. We are not aware that any legislation has granted the Agency authority over pharmacy practice or the state boards; and the profession is not prepared to defer to the Agency on issues of pharmacy practice.

⁶ Food and Drug Administration. “Compliance Policy Guides Manual Sec. 460.200” accessed on 01/18/08 at http://www.fda.gov/OHRMS/DOCKETS/98fr/02D-0242_gdl0001.pdf

⁷ FDCA § 503A(b)(i)(II).

Thank you for your consideration of the views of the nation's pharmacists. We would appreciate the opportunity to discuss these issues with you. We believe that the Agency's approach may unnecessarily limit patient access to necessary medications.

Sincerely,

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