



February 5, 2008

Andrew C. von Eschenbach, MD, Commissioner
Office of the Commissioner, HFA-305
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: IACP Response to FDA Actions Against BHRT

Dear Commissioner Eschenbach:

As Executive Director of the International Academy of Compounding Pharmacists (“IACP”),¹ I am writing to convey IACP’s deep concerns with regard to FDA’s recent actions against compounded bio-identical hormone replacement therapy (“BHRT”) drugs.² These actions include the January 7, 2008 issuance of seven Warning Letters to pharmacies that compound BHRT; FDA’s January 9, 2008 response to a 2005 Citizen Petition submitted by a manufacturer of FDA-approved HRT products; public statements by FDA officials in a January 9, 2008 press conference discussing the agency’s actions against BHRT; and the agency’s January 9 press release and referenced

¹ IACP is a non-profit association of more than 2,000 members devoted to the protection and advancement of pharmaceutical compounding. Collectively, IACP’s member pharmacists compound millions of doses each year to fill prescriptions from physicians and veterinarians. As the only association broadly representing United States compounding pharmacies, IACP has a vital interest in ensuring that pharmacies can continue to fill prescriptions for compounded drugs, which has long been a key component of pharmacy practice and the health care system in this country.

² The pharmacy profession also joined together to object to FDA’s recent actions in a letter sent February 1, 2008 to the Commissioner’s office. The American Pharmacists Association, IACP, the National Community Pharmacists Association, the National Alliance of State Pharmacy Associations, and the American College of Apothecaries united to decry FDA’s intervention in pharmacy practice and FDA’s actions to unnecessarily limit patient access to necessary medications. Combined, the organizations represent more than 125,000 members, including 23,000 community-based pharmacies and the 50 state pharmacy associations.

website materials, all declaring that compounded BHRT products are unlawful. In IACP's view, these closely coordinated agency actions (taken the same week as the Fifth Circuit oral argument in Medical Center Pharmacy v. Gonzales) constitute an unjustified attack on the fundamental right of pharmacists to compound physician-ordered drugs for patients who depend on them. We are also very concerned that this attack was triggered by a request for enforcement action by a drug company with a commercial interest in suppressing compounding, and that FDA has declined to acknowledge the relationship between FDA's actions and the manufacturer's requests.

An FDA official stated emphatically during the January 9 press conference that “[c]learly, and without any confusion, we are not taking today's action as a result of the Wyeth Citizen Petition [T]he action today is distinct and a stand-alone initiative.” A different FDA official later admitted that it was indeed FDA's intent “to bundle the Warning Letters together with the article and with the Citizen Petition response . . . to get the word out . . . that FDA has concerns about these products.” It strains credulity for FDA to deny that the issuance of the Warning Letters two days before its response to Wyeth's petition was wholly unrelated to and unmotivated by the Petition. IACP is concerned that FDA's recent actions have been unduly influenced by Wyeth.

It would also be disingenuous for FDA to say that the timing of these actions was unrelated to the timing of the Fifth Circuit Court of Appeals oral argument. By letter dated January 23, 2008, the Department of Justice filed a copy of the FDA's Citizen Petition response with the Fifth Circuit. Given that Wyeth filed an amicus brief with the Fifth Circuit in the same case, and that FDA responded to a citizen petition filed more than two years earlier, FDA's actions on January 7 and 9 do not appear to be mere coincidence.

FDA has stated that its principal concerns are compounded BHRT marketed with what it considers to be false and misleading claims, and compounded BHRT containing

the ingredient estriol. FDA has stated that it does not intend to put a stop to all compounding of BHRT. Nevertheless, the public impact of FDA's actions is immense and should not be understated. According to conservative estimates, at least 80% of all compounded BHRT prescriptions incorporate the ingredient estriol. Physicians currently prescribe these estriol-containing preparations for many of thousands of women. Some third party payors have discontinued coverage of compounded estriol because of FDA's actions. As a result of FDA's unwarranted actions, countless women and their doctors will be forced to seek other, less optimal solutions for no good reason.

IACP urgently requests a meeting with you and your staff to discuss these critical issues.

Pharmacy compounding is lawful and compounded drugs are not "new drugs"

The seven January 7, 2008 BHRT Warning Letters, like most Warning Letters FDA has issued to compounding pharmacies in recent years, assert that all compounded drugs are "new drugs," and therefore unlawful, because they have not been reviewed or approved by FDA.³ While FDA claims to rely on "substantial judicial authority" for its position, none of the cases cited by the agency actually hold that compounded drugs are unapproved new drugs. FDA's adverse position toward pharmacy compounding as expressed in the January 7, 2008 Warning Letters is not new.

What is new, but which the agency buries in a footnote, is a highly pertinent ruling by the only federal court to have directly addressed the determinative legal question of whether compounded drugs are "new drugs" under the Federal Food, Drug, and Cosmetic Act ("FDC Act"). Medical Center Pharmacy v. Gonzales, 451 F. Supp. 2d 854 (W.D.

³ The discussion of FDA's position on compounded drugs contained in warning letters to compounding pharmacies is nearly identical in the agency's January 9 response to the Wyeth Citizen Petition requesting FDA to take action against compounded BHRT drugs.

Tex. 2006). The Medical Center Pharmacy court held, significantly, and in direct contrast to FDA's view, that compounded drugs are not new drugs under the FDC Act. Id. at 856. The court reached that decision based on its analysis of "relevant case and statutory law, as well as legislative intent." Id. at 858. In the January 7 Warning Letters, FDA mentions this case in a footnote, and is quick to note that an appeal is pending, but it fails to mention the substance of the court's holding, or to acknowledge that the decision is unfavorable to its position that all compounded drugs are unlawful "new drugs." FDA's release of the Warning Letters and reply to Wyeth immediately before oral argument on FDA's appeal – and its subsequent submission to the court of its reply to Wyeth – appear to be calculated efforts to try to assist FDA in its appeal. It is ironic that FDA's discussion of the law alleging that drugs are misbranded for failure to provide complete disclosures would itself glide over the most relevant court case.

If, as FDA claims, all compounded drugs are new drugs under the FDC Act, then it necessarily follows – notwithstanding the agency's decision to exercise enforcement discretion – that every act of pharmacy compounding performed since 1938 has, as a matter of law, been a violation of the Act. This is true whether a pharmacist is compounding BHRT because the patient's physician believes this to be the best option for the patient or, as one of the judges noted during oral argument in the Medical Center case, whether MD Anderson compounds a medication for a cancer patient. All compounding is illegal under FDA's theory. FDA takes this view even though Congress has authorized and supported compounding for decades.

The agency has repeatedly sought to brush off the consequences of its interpretation. By citing its enforcement discretion, FDA brands as alarmist those who note that FDA's theory means compounding is illegal. IACP acknowledges that FDA is not routinely taking enforcement action based on its view that all compounded drugs are unapproved new drugs. Yet FDA itself has refused to acknowledge that the agency's construction of the FDC Act does mean every act of compounding is unlawful.

Unfortunately, the consequences of FDA's position are broad and harm all compounding pharmacists and, more importantly, their patients. No matter how carefully the FDA exercises its enforcement discretion, having one's profession declared illegal by a federal agency is neither harmless nor inconsequential. This characterization confuses and alarms patients, especially as media outlets repeatedly propagate FDA's position. Branding compounding as "illegal" could well induce patients to avoid the use of compounded medications that prescribers have determined are medically necessary and for which there are no commercially available alternatives. Furthermore, the FDA's position has led organizations, both corporations and associations, to adopt bold anti-compounding policies. For example, to the detriment of many patients, Genentech recently stopped selling Avastin to compounding pharmacies, largely justifying its position based on FDA policy and an FDA Warning Letter questioning the legality of pharmacists to compound Avastin. Insurers, such as Aetna and Blue Cross/Blue Shield, have cited FDA policy in denying coverage to patients for compounded medications. FDA's policy that compounding is illegal has also created additional difficulties for pharmacies in obtaining required liability insurance for compounding.

Exercising enforcement discretion towards an activity that is considered illegal is not the same as saying that an activity is lawful. FDA's issuance of the seven Warning Letters and its press conference, with the attendant widespread publicity, further propagates this perspective that compounded drugs violate the law. Therefore, IACP remains deeply troubled by FDA's repeated public assertions that compounded drugs are unapproved new drugs.

Compounded BHRT drugs containing estriol are lawful

Relying on certain “factors” articulated in its controversial Compliance Policy Guide (“CPG”),⁴ FDA states in the BHRT Warning Letters that it is “prepared to take enforcement action to halt . . . [the] compounding of drugs containing estriol” because estriol is not a component of any FDA-approved drug, and the use of estriol in BHRT is not sanctioned in an FDA-approved IND. Agency officials participating in the January 9 press conference similarly avowed that FDA would not allow pharmacies to continue compounding BHRT products that contain estriol.

Estriol, compared to other estrogenic compounds, is a relatively weak, naturally-occurring hormone produced by women, especially during the third trimester of pregnancy. Estriol has been approved and marketed for more than 40 years in Europe and Asia for the treatment of post-menopausal symptoms. Such drugs include, for example, Organon’s Ovestin and Janssen’s Ortho-Gynest. Even Wyeth, which urged FDA to act against estriol-containing BHRT products on grounds that “their sale without prior FDA approval . . . violates the new drug provisions of the Act and poses a serious threat to public health” (Wyeth Petition at 19 (emphasis added)) markets two estriol-containing menopause drugs in Germany called Cyclo-Menorette® and Estriolsalbe®.

While estriol is not a component of any FDA-approved drug product now on the U.S. market, the 1940 edition of an American Medical Association (“AMA”) publication listing “articles . . . accepted by the AMA Council on Pharmacy and Chemistry” documents that estriol has been used to treat menopause and other estrogen deficiency-related conditions since at least 1940. AMA, New and Nonofficial Remedies (1940 ed), 369-70. The same AMA publication also shows that in 1940, estriol was marketed by at

⁴ FDA issued the current CPG in 2002. It did so without first soliciting comments from stakeholders. The agency received many critical comments afterwards. For more than five years, FDA has been promising to issue a new CPG, but has not yet done so. IACP, along with many members of Congress, has urged FDA to issue a new draft guidance to allow for meaningful public comment.

least three U.S. suppliers. *Id.* at 370-71. More significantly, estriol has been the subject of an official U.S. Pharmacopeia (“USP”) monograph since 1980.

Notwithstanding FDA’s claim that drugs used for compounding must be components of FDA-approved drugs, there is nothing illegal about compounding with estriol or other drug substances that are not components of FDA-approved drugs. Compounding is and always has been a lawful and essential part of pharmacy practice. Nothing in the FDC Act, or in any state law governing pharmacy practice, says compounding must be carried out using only components of FDA-approved drugs. Nor does the FDC Act authorize FDA to adopt such a requirement. Indeed, Congress could not have expected pharmacists in 1938 to compound only with drugs that were components of FDA-approved drug, given that in 1938, when the FDC Act was enacted, there were no FDA-approved drugs. It simply cannot be the case that in 1938, all compounded drugs suddenly became unlawful and subject to enforcement action because they had been made with components not included in any FDA-approved drug.

Moreover, as Congress declared when it passed the Food and Drug Administration Modernization Act of 1997 (“FDAMA”), adding section 503A to the FDC Act, a drug product may be compounded by a licensed pharmacist using bulk drug substances – such as estriol – that “comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists.” 21 U.S.C. §353a(b)(1)(A)(i)(I). In short, it is Congress’s explicit intent that drugs subject to and in compliance with a USP monograph be allowed for use in compounding notwithstanding whether they are components of FDA-approved drug products.⁵ Estriol is a USP monograph drug. Further,

⁵ Whether §503A continues to be part of the FDC Act in the wake of Thompson v. Western States Medical Center, 535 U.S. 357 (2002) has no bearing on this provision’s status as a clear and valid expression of congressional intent that USP monograph drugs be permitted for use in compounding even if they are not components of any FDA-approved drug. Moreover, the district court stated in Medical Center Pharmacy that §503A was in place, with the sole exception of the advertising provisions. The Fifth Circuit has directed additional briefing on this point. Given this background, it is inappropriate for FDA to disregard the

Congress, in the FDC Act, recognized the United States Pharmacopeia (USP) as the official compendium and standards-setting authority for all drugs and healthcare products manufactured and sold in the United States. USP standards for pharmacy compounding clearly permit the use of estriol. FDA's position is more restrictive than FDAMA or USP standards and impermissibly conflicts with congressional intent.

FDA's CPG is not a law or a regulation, and it does not establish any binding legal obligations. Moreover, FDA has, in the case of the seven recently-issued Warning Letters, erroneously invoked its own policy as the basis for the prohibition. In the CPG, FDA makes clear that "traditional compounding" – the extemporaneous compounding of reasonable quantities of human drugs upon the receipt of a valid prescription for an individual patient – "is not the subject of this guidance." Rather, the purpose of the CPG is to help FDA determine when to consider enforcement action against a pharmacy that is "manufacturing" "clearly outside the bounds of traditional pharmacy practice." The "factors" enunciated in the CPG, therefore, are factors to be considered when a pharmacy is suspected to be "manufacturing" beyond the bounds of traditional compounding. There is nothing in the seven Warning Letters suggesting that FDA believed any of these pharmacies to be manufacturing. The use of estriol – or any other individual ingredient – is irrelevant to the issue of whether a compounding pharmacy is acting like a manufacturer.

Furthermore, the CPG does not have the force of law or regulation. In 1995, the United States Court of Appeals for the Fifth Circuit held that the 1992 CPG was not a substantive rule.⁶ 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. However, FDA is now relying on its policy in taking action against pharmacies.

USP monograph status of estriol and its long-standing use in the United States.

⁶ *Professionals and Patients for Customize Care v. Shalala*, 56 F.3d 592 (1995)

FDA has not presented or claimed to possess any actual evidence that estriol is unsafe for use in compounded hormone replacement therapy. As one FDA official acknowledged during the press conference: “We do not have information that speaks to whether [BHRT drugs containing estriol] are safe or effective. That information is simply unavailable to the agency.” FDA officials further acknowledged that the agency has not received any reports or other information concerning adverse events caused by estriol-containing BHRT preparations. It is inconsistent for FDA to impose a burden on pharmacies of establishing that compounded BHRT products containing estriol are safe and effective, while FDA attacks BHRT compounding without any evidence that compounded BHRT drugs containing estriol pose a harm to public health. These assaults are particularly unjustified given that the company that precipitated the Warning Letter is selling an estriol-based product.

Finally, it is also important to note that compounded medicines are prepared for individual patients at the explicit direction of their physicians. No preparation containing estriol is compounded without a prescription from a physician, who has evaluated the particular patient, the risks and benefits of the therapy and made an informed decision to prescribe that preparation.

Use of the term “bio-identical” is lawful and appropriate absent FDA evidence to the contrary

In the BHRT Warning Letters, and as noted during the press conference, FDA claims that use of the term “bio-identical” to describe pharmacy-compounded hormone therapy products is false and misleading because it “implies that [such] compounded hormone therapy drugs are natural, or identical to the hormones made by the body” and the agency is “unaware of substantial evidence (consisting of adequate and well controlled clinical investigations)” to support this claim. FDA further states in its

January 9 press release that it regards “bio-identical” to be “a marketing term implying a benefit for the drug, for which there is no medical or scientific basis.”

IACP submits that FDA is improperly conflating a concern about the meaning of the term “bio-identical” with its separate concerns about the claims individual pharmacies have made for BHRT products. IACP does not support unfounded health, safety or efficacy claims attributed to BHRT. However, whatever claims have been made by individual pharmacies for these formulations has no bearing on the permissibility of the term “bio-identical.” This term, in and of itself, is not false or misleading, and does not cause compounded BHRT drugs to be misbranded. It is simply a term that compounding pharmacies – and manufacturers of FDA-approved drugs⁷ – use to convey that the chemical structure of a component is identical or nearly identical to a substance that occurs naturally in the body. FDA has provided no evidence that the term “bio-identical” impermissibly implies any benefit, as opposed to simply describing an attribute of the product.

Moreover, it is the agency, and not the pharmacies, which bears the burden under the FDC Act of establishing that the use of a term to describe a product is false and misleading. An article is not “misbranded” under the FDC Act simply because the agency says so; rather, as established by federal case law, FDA must show that a product description or claim is false or misleading. It is wrong for FDA to baldly assert that use of the term “bio-identical” constitutes misbranding because of some implication that FDA perceives, and then require the recipients of the accusation to prove the negative.

⁷ For example, the FDA-approved labeling for Prometrium® (Progesterone, USP) Capsules states that the synthesized progesterone in this drug is “chemically identical to progesterone of human ovarian origin.” Solvay, the manufacturer of this product, notes on its website that Prometrium® is “bio-identical to the progesterone that is naturally produced by your own body.” www.prometrium.com (last visited Jan 29, 2008). Ascend Therapeutics similarly claims on its website for EstroGel® (estradiol gel) that EstroGel is “bio-identical estrogen replacement therapy that comes from a plant source . . . the estrogen in EstroGel is similar to the one your body produces naturally.” www.estrogel.com (last visited Jan 29, 2008).

Conclusion

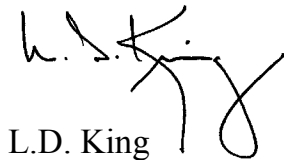
FDA faces many challenges and limited resources. As exemplified by the recent Warning Letters, press conference, and response to Wyeth, FDA has devoted considerable efforts to regulating pharmacy compounding.

IACP has long been committed to developing an appropriate regulatory framework for compounding. However, we believe it is counterproductive for FDA to publicly attack the compounding profession the way it did in the recent Warning Letters and press conference. FDA's recent actions have broad implications for thousands of patients, whose access to medications that their doctors have prescribed is threatened without any public health justification.

We believe that additional discussions may help the agency develop policies relating to compounding that will result in better allocating its limited resources. We would like to meet with you as soon as possible to discuss these important issues.

I will contact your office shortly to arrange a meeting.

Sincerely,

A handwritten signature in black ink, appearing to read "L.D. King". The signature is stylized with a large, sweeping "K" and a long horizontal stroke.

L.D. King
Executive Director, EVP