



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JAN 9 2008

Andrew S. Krulwich
Benjamin B. Reed
Sarah E. Botha
Wiley Rein & Fielding LLP
1776 K Street, N.W.
Washington, D.C. 20006

RE: Docket No. 2005P-0411/CP1 & SUP1

Dear Messrs. Krulwich and Reed and Ms. Botha:

This responds to your citizen petition dated October 6, 2005 (Petition), submitted on behalf of Wyeth. In the petition, you request that the Food and Drug Administration (FDA) take the following actions with respect to pharmacies engaged in the compounding of so-called *bio-identical hormone replacement therapy* (BHRT)¹ drugs:

1. Initiate enforcement action, in the form of seizures, injunctions and/or warning letters, against any BHRT compounding pharmacies whose facilities or whose manufacturing, labeling, advertising, or dispensing practices FDA determines are in violation of the Federal Food, Drug, and Cosmetic Act (FDCA).
2. Commence investigations to determine whether entities involved either in dispensing compounded BHRT drugs or in promoting such drugs are providing a proper patient package insert (PPI) with each package that is intended to be dispensed to a patient and are including material facts and risk information in all labeling and advertisements provided to patients and health care professionals or directed to the consumer population at large, including the following:
 - That the BHRT drug is a new drug and does not have FDA approval;

¹ We use the term *BHRT* in this petition response because that is the term used in the citizen petition and generally used by compounding pharmacies. FDA uses the term *hormone therapy* rather than the term *hormone replacement therapy* because FDA no longer considers the use of the word *replacement* to be technically correct when referring to hormone therapy for menopause. The term *bio-identical* has no accepted scientific meaning.

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- That the BHRT drug is/was compounded, or prepared, in a pharmacy that is not required to comply with FDA current good manufacturing practice (CGMP) requirements; and
 - That the BHRT drug has not been demonstrated to be safe or effective for any use, or safer or more effective than FDA-approved hormone therapy drugs.
3. Require that all labeling and advertisements explain the material facts and all risk information relating to the BHRT drug, that consumer-related materials be written in language that will be easily comprehensible by laypersons, and that all comparative or superiority claims be appropriately supported by legitimate and sufficient data.
 4. Require BHRT pharmacies that have failed to provide material facts and/or risk information in labeling and advertisements to take certain mitigating actions.
 5. Issue an Alert or Talk Paper regarding compounded BHRT drugs directed to consumers, health care providers, and the compounding industry.

We have carefully reviewed your petition and the supplement to the petition dated April 4, 2006 (Supplement), as well as other information available to the Agency. We also reviewed numerous comments on the petition submitted by pharmacies, pharmacy trade associations, consumer health care and professional organizations, health care practitioners, and individual citizens.²

Decisions with respect to initiating enforcement actions are generally made on a case-by-case basis and are within the discretion of the Agency.³ Requests for the Agency to initiate enforcement actions are not within the scope of FDA's citizen petition procedures.⁴ *See* 21 CFR 10.30(k). For this reason, and for the reasons stated below, your petition is granted in part and denied in part.

² More than 70,000 comments (including at least 14,000 form letters) have been submitted on this petition. Comments submitted by John A. Sunycz, M.D., dated October 24, 2005 (2005P-0116/EMC6), and the National Women's Health Network, dated November 4, 2005 (2005P-0116/C5), were submitted to a different docket, but refer to BHRT drugs available through compounding pharmacies. These comments were not relevant to Docket No. 2005P-0116, but are considered in the context of this petition, which addresses compounded BHRT drugs directly.

³ FDA was considering issues related to compounded BRHT drugs prior to receipt of your petition. We note that we are issuing warning letters to certain compounding pharmacies for violations relating to compounded BHRT drugs.

⁴ Therefore, your request that FDA initiate enforcement action against BHRT compounding pharmacies that violate the FDCA, in the form of seizures, injunctions, and/or warning letters, is denied. In addition, to the extent you request that FDA take enforcement action with respect to those specific activities you describe, such as labeling and advertising that fall outside the scope of traditional pharmacy compounding, such requests are also denied.

I. BACKGROUND

A. Hormone Therapy

During menopause, women may have lower levels of the hormones estrogen and progesterone and may experience hot flashes, night sweats, vaginal dryness, and bone loss. To help with these symptoms, some women take hormones such as estrogen or estrogen with a progestogen (i.e., progesterone or a progestin)⁵ after consultation with and a prescription from their physicians. Estrogen and estrogen with a progestogen remain the most effective drugs available to treat hot flashes and vaginal symptoms of menopause. In addition, hormones may reduce the chance of getting weak bones (which break easily).

FDA has approved drugs for use in hormone therapy (HT) for menopause symptoms, and advises women who choose to use hormones to use them for the shortest time necessary at the lowest dose that helps, in consultation with their physicians. However, like all medicines, HT drugs have risks. For some women, HT may increase their chance of getting blood clots, heart attacks, strokes, breast cancer, and gallbladder disease. For a woman with a uterus, estrogen increases the chance of getting endometrial cancer (cancer of the uterine lining). Adding a progestin or progesterone lowers this risk.

The National Institutes of Health (NIH) Women's Health Initiative (WHI) conducted several studies, including a large study to determine the effects of estrogen with the progestin medroxyprogesterone acetate (MPA) on the prevention of heart disease. The subjects of the study were not taking the medication for an FDA-approved use. The study was halted in 2002 because the health risks appeared to outweigh the benefits for participants taking estrogen with progestin. Results from this study showed that postmenopausal women taking estrogen with a progestin had an increased risk of heart attack, stroke, breast cancer, and blood clots. The initial publication of the study findings reported that the absolute excess risks per 10,000 women-years in the group treated with the combination estrogen/progestin product were 7 more heart attacks, 8 more strokes, 18 more blood clots, and 8 more invasive breast cancers than in the placebo control group. Conversely, the absolute risk reductions per 10,000 women-years for the estrogen/progestin group were 6 fewer colorectal cancers and 5 fewer hip fractures than the placebo group.

As a result of the WHI hormone studies, FDA requested changes to the existing black box warning⁶ in FDA-approved labeling for estrogen-alone drugs and requested that a black box warning be added to the FDA-approved labeling for combination estrogen/progestin drugs. In addition, FDA requested that a black box warning be added to the FDA-approved labeling for progestin-alone drugs approved for use in combination

⁵ Progestin is a synthetic hormone that has progesterone-like activity. Synthetic drug products having progestational activity (biologic activity similar to progesterone in the body) are referred to by several names, including progestins, progestogens, gestogens and progestational hormones.

⁶ A black box warning is designed to warn of serious adverse reactions that may lead to death or serious injury. See 21 CFR 201.57(c)(1).

with estrogen because the progestin-alone drugs are frequently used concomitantly with estrogen-alone drugs and would therefore share the same or similar risks as fixed-dose combination estrogen/progestin drugs. In general, the warnings highlight that the WHI study reported increased risks of heart attack, stroke, breast cancer, and blood clots, and because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

B. Compounded BHRT Drugs

In the past several years, there has been a dramatic increase in the sale of drugs described as bio-identical hormones.⁷ The term *bio-identical* is a marketing term that has no defined meaning in any medical or conventional dictionary. The term is often used by compounders in conjunction with the term *natural* to describe hormone-like substances derived from plants that are chemically altered to mimic endogenous hormones (e.g., estrone, estriol, estradiol, progesterone) that exist in the human body.

The potential public health risks from compounded BHRT drugs are significant. Compounded BHRT drugs have not been demonstrated to be safe and effective. Many of these compounded BHRT drugs are labeled and advertised as having benefits that have been definitively disproved or for which there is no evidence. Furthermore, there are no scientific data to support the contention that compounded BHRT drugs carry fewer risks for women than FDA-approved prescription hormone therapy drugs. Claims that are false or misleading can have significant health consequences for women.

C. Agency Policy on 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.⁸ Traditional compounding is used to prepare medications that are not FDA-approved, such as a drug for a patient who is allergic to an ingredient in a mass-produced drug or alternate dosages for children.

The FDCA establishes Agency jurisdiction over "new drugs." Compounded drugs are "new drugs" within the meaning of section 201(p) of the FDCA (21 U.S.C. 321(p)) because they are not "generally recognized, among experts . . . as safe and effective" for their labeled uses.⁹ There is substantial judicial authority supporting FDA's position that

⁷ BHRT drugs are a diverse group of drugs produced by compounding pharmacies.

⁸ See *Thompson v. Western States Medical Center*, 535 U.S. 357, 360-61 (2002).

⁹ See *Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609, 619, 629-30 (1973) (explaining the definition of "new drug").

compounded drugs are not exempt from the new drug definition.¹⁰ Because they are new drugs under the FDCA, compounded drugs may not be introduced into interstate commerce without FDA approval.¹¹

The drugs that pharmacists compound generally are not FDA-approved and lack an FDA finding of safety and efficacy. However, FDA has long recognized the important public health function served by traditional pharmacy compounding.

Through the exercise of enforcement discretion, FDA historically has declined to take 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 drug manufacturers and whose compounding practices result in significant violations of the adulteration, misbranding, or new drug provisions of the FDCA.¹²

FDA's current enforcement policy with respect to pharmacy compounding is articulated in the Compliance Policy Guide (CPG), *Sect. 460.200 Pharmacy Compounding* (compounding CPG), issued by FDA on May 29, 2002 (*see* 67 FR 39409, June 7, 2002).¹³ The compounding CPG identifies factors that the Agency considers in deciding whether to initiate enforcement action with respect to compounding. These factors help

¹⁰ *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.").

¹¹ In August 2006, however, 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*, 451 F.Supp.2d 854 (W.D. Tex. August 30, 2006). That court has ruled that compounded drugs are not subject to the new drug definition of the FDCA. The government has appealed this decision to the Court of Appeals for the Fifth Circuit. Furthermore, in a comment submitted on this petition, the International Academy of Compounding Pharmacists (2005P-0411/C3088) refers to the U.S. Supreme Court's decision in *Gonzales v. Oregon*, 546 U.S. 243 (2006), to assert that FDA lacks the authority to regulate compounded drugs. This court case, which addresses provisions of the Controlled Substances Act, is inapplicable here because, as previously stated, the FDCA establishes FDA jurisdiction over "new drugs," including compounded drugs.

¹² *See* sections 501, 502, and 505 of the FDCA (21 U.S.C. 351, 352, and 355).

¹³ 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), which stated that section 503A included unconstitutional restrictions on commercial speech and those restrictions could not be severed from the rest of section 503A. In *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), the Supreme Court affirmed the Ninth Circuit ruling that the restrictions in question violated the First Amendment, but it did not consider whether these restrictions could be severed from the rest of section 503A. FDA shares the Ninth Circuit's view that section 503A is now void.

differentiate the traditional practice of pharmacy compounding from the manufacture of unapproved new drugs. As stated in the compounding CPG, the “list of factors is not intended to be exhaustive.”

The factors identified in the compounding CPG include whether a pharmacy is:

- compounding drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions;
- compounding drugs for third parties who resell them to individual patients or offering compounded drugs at wholesale to other state-licensed persons or commercial entities for resale;
- compounding drugs that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drugs. However, in certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a drug that is only slightly different from an FDA-approved drug that is commercially available. In these circumstances, FDA will consider whether there is documentation of the medical need for the particular variation of the compound for the particular patient; and
- compounding finished drugs from bulk active ingredients that are not components of FDA-approved drugs without an FDA-sanctioned investigational new drug application (IND).

These are some of the factors that help guide FDA's enforcement decisions and thus describe the kinds of conduct related to compounding that the Agency generally regards as most inappropriate. Since the compounding CPG was issued in 2002, FDA has received and reviewed public comments submitted in response to the CPG and is in the process of revising its guidance on pharmacy compounding.

II. DISCUSSION OF ISSUES

In your petition, you raise a number of concerns to support your requests regarding compounded BHRT drugs. We address your concerns in section II.A of this response and respond to your requests in section II.B.

A. Concerns Raised About Compounded BHRT Drugs

1. Activities That Fall Outside Traditional Pharmacy Compounding

You state that BHRT pharmacies are compounding drugs that are essentially copies of FDA-approved hormone drugs because the change from the ingredients used in FDA-approved hormone drugs to ingredients used in the compounded BHRT drugs does not create a significant difference for a patient using the compounded BHRT drug. In addition, you state that BHRT pharmacies are not compounding variations of FDA-approved hormone products based on the specific medical needs of particular patients (Petition at 21). Furthermore, you state that some compounding pharmacies

substitute compounded BHRT drugs when filling prescriptions for prescribed FDA-approved HT drugs (Petition 9-10).¹⁴ You conclude that for these reasons many BHRT pharmacies are engaged in drug manufacturing rather than traditional compounding. (Petition 22.)

We note that compounding copies and near copies of FDA-approved drugs is an activity that falls outside the bounds of traditional pharmacy practice and raises the kinds of concerns normally associated with drug manufacturing. As stated in the compounding CPG, FDA will consider the compounding of copies or near copies, as well as other factors listed in the CPG, in deciding whether to take enforcement action in individual cases. We also note that you have not provided specific evidence that compounding pharmacies substitute compounded BHRT drugs when filling prescriptions for FDA-approved products.

2. *Use of Unapproved Drugs*

You state in the petition that some of the BHRT drugs advertised contain an active ingredient (estriol) that is not a component of any FDA-approved drug, raising additional public health and safety concerns for women taking these drugs (Petition at 17). Furthermore, you state that by using estriol in compounded BHRT drugs, compounding pharmacies are engaging in manufacturing new, unapproved drugs rather than traditional compounding activities (Petition at 17-18).

We note that as described in the compounding CPG, one of the factors that the Agency will consider in determining whether the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer is whether the pharmacy is compounding finished drugs from bulk active ingredients that are not components of FDA-approved drugs without an FDA-sanctioned IND. We agree that estriol, a form of estrogen, is not an ingredient in any drug approved by FDA. As stated in the compounding CPG, FDA will consider the compounding of drugs with ingredients not found in approved drugs, as well as other factors listed in the CPG, in deciding whether to take enforcement action in individual cases.

3. *Other Potential Health Risks*

In addition to your concerns regarding the use of unapproved drugs, you raise concerns about the failure of compounding pharmacies to adhere to the CGMP requirements of section 501(a)(2)(B) of the FDCA and suggest that many compounded BHRT drugs would likely fail standard quality tests and perhaps potency testing (Petition at 34-35).

We note that drugs compounded by pharmacies must meet the CGMP requirement of section 501(a)(2)(B) of the FDCA, as well as the quality and potency requirement of section 501(c) of the FDCA. As described in the compounding CPG, FDA will consider

¹⁴ FDA considers drug products to be therapeutically equivalent only if they are shown to be pharmaceutically equivalent (same active ingredients) and bioequivalent (behave the same way in the body).

enforcement action when the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the FDCA, including violation of these adulteration provisions.

4. *Exemptions from Adequate Directions for Use*

You state that the labeling for compounded BHRT drugs violates the adequate directions for use requirement in section 502(f)(1) of the FDCA, and that compounded BHRT drugs that do not comply with this requirement or qualify for the exemption at 21 CFR 201.100 are misbranded (Petition at 23-24, Supplement at 14-15).

We note that a compounded drug, prior to dispensing, is misbranded under section 502(f)(1) of the FDCA if its labeling fails to bear adequate directions for use and it does not qualify for an exemption from that requirement under 21 CFR 201.100 or 201.115. Furthermore, at the time the compounded drug is dispensed to the patient, it is exempt from some of the labeling requirements in section 502 of the FDCA, provided that the label contains the information identified in section 503(b)(2) (21 U.S.C. 353(b)(2)). However, the exemption in section 503(b)(2) does not exempt a compounded drug from section 502(a) of the FDCA, which deems a drug misbranded if its labeling is "false or misleading in any particular."

B. Requests Regarding Compounded BHRT Drugs

1. *Patient Package Inserts*

In the petition, you ask FDA to require all pharmacies involved in dispensing compounded BHRT drugs to include certain material facts in their labeling and to provide PPIs with each package intended to be dispensed to a patient pursuant to § 310.515 (Petition at 4-5, 27). You suggest in the petition that compounded BHRT drugs are often dispensed without proper PPIs. You conclude that any pharmacy that is not including a PPI with its compounded estrogen product is dispensing a misbranded product under section 502(a) of the FDCA (Petition at 27).

FDA generally does not impose affirmative labeling requirements for compounded drugs made within the scope of traditional compounding. However, it has always been FDA's position that pharmacies providing compounded drugs should also provide proper risk information to consumers and comply with the statutory requirements applicable to drugs. In particular, we reiterate that under section 502(a) of the FDCA, a drug, including a compounded drug, is deemed to be misbranded if its labeling is false or misleading.

2. *Promotional Activities*

You state in the petition that compounded BHRT drugs contain estrogen ingredients to which specific risks have been attributed by FDA and the WHI study, but that patients using these drugs receive little or no information about the potential risks of these drugs

(Petition at 9). You also state that compounding pharmacies promote compounded BHRT drugs as wholesale substitutes for FDA-approved HT drugs, and that by marketing their compounded drugs in this manner, compounding pharmacists are manufacturers subject to the new drug, adulteration, and misbranding provisions of the FDCA (Petition at 19-20). Furthermore, you state that compounded BHRT drugs are being promoted in a misleading manner and that you believe these drugs are prescribed based on misleading promotional activities (Petition at 22-34). You conclude that such actions by compounding pharmacies render their compounded drug products to be misbranded under the FDCA (Petition at 22-34) and that FDA must take action against such practices.

Under the FDCA, false or misleading or otherwise violative advertising causes a drug to be considered a misbranded drug (section 502(n) of the FDCA, 21 CFR part 202). In addition, under section 502(a) of the FDCA, drugs are considered to be misbranded if their labeling is false or misleading in any particular. Among other things, section 201(n) of the FDCA provides that, in determining whether advertising or labeling misbrands a drug, FDA may consider both representations made about the drug and the extent to which the material at issue fails to reveal facts that are material in light of these representations or the risks associated with the drug (*see* § 202.1(e)(5)).

In addition, promotion for a compounded BHRT drug cannot contain claims of less risk or greater benefit than FDA-approved drugs absent substantial evidence or substantial clinical experience to support such claims (*see* § 202.1(e)(6)(i)).

FDA has reviewed the information submitted with your Petition as well as other information available to the Agency. In doing so, we find the following:

- We are aware of no scientific data to support the contention that compounded BHRT drugs are associated with fewer risks to women or are likely to be safer, as effective, or more effective than FDA-approved prescription hormone therapy drugs.
- We are aware of no adequate randomized, prospective, controlled clinical trials of compounded BHRT drugs that either demonstrate that they are better at relieving menopausal symptoms than a placebo, or that compare them to an FDA-approved drug and establish that the compounded drugs work equally well.

In addition, the Agency has concluded that other claims regarding benefits of BHRT drugs have either been definitively disproved (e.g., prevention of heart attacks) or are not supported by substantial evidence (e.g., lower incidence or prevention of uterine cancer or breast cancer).

3. *Corrective Actions*

In your petition, you request FDA enforcement action, in the form of seizures, injunctions and/or warning letters, against any BHRT compounding pharmacies whose facilities or whose manufacturing, labeling, advertising, or dispensing practices FDA determines are in violation of the FDCA (Petition at 3). You also request that FDA require BHRT

compounding pharmacies that failed to provide material facts and/or risk information in labeling and advertisements to take steps to notify each health care provider who submitted a prescription, and each patient to whom compounded BHRT drugs were dispensed, that the information was not provided, as well as post a correction at the pharmacy counter (Petition at 4-5).

As stated previously, decisions with respect to enforcement actions are generally made by the Agency on a case-by-case basis after evaluation of an individual firm's operations and not in a citizen petition response.¹⁵

4. *Information for the Public*

You request that the FDA issue an Alert or Talk Paper regarding compounded BHRT drugs that would, among other things, notify consumers, health care providers, and pharmacies concerning the safety and effectiveness of these drugs (Petition at 5-6). We believe that public education about compounded BHRT drugs is important, and we are working to convey important information to health care providers, patients, and pharmacy operations. We have developed a public awareness campaign about BHRT for indications including the treatment of menopausal symptoms. As a part of this public awareness campaign, we are releasing an article, which will be published on the FDA's Consumer Health Information Web page, entitled "Bio-Identicals: Sorting Myths from Facts." In addition, we are issuing a press release and a Frequently Asked Questions (FAQs) document and are arranging telephone calls with the media and stakeholders to discuss these issues.

III. CONCLUSION

Although we share many of your concerns about compounded BHRT drugs, we cannot grant all your requests. We have developed a public awareness campaign about BHRT for indications including the treatment of menopausal symptoms. We are releasing a consumer article, issuing a press release and FAQs document, and arranging calls with the media and stakeholders to discuss these issues. For the reasons stated above, your petition is granted in part and denied in part.

Sincerely,



Margaret O'K Glavin
Associate Commissioner
for Regulatory Affairs

¹⁵ See note 3, supra.