DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

STATEMENT BY

STEVEN K. GALSON, M.D., M.P.H.

DIRECTOR

CENTER FOR DRUG EVALUATION AND RESEARCH

U.S. FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SENATE SPECIAL COMMITTEE ON AGING

HEARING ON

BIO-IDENTICAL HORMONES: SOUND SCIENCE OR BAD MEDICINE?

APRIL 19, 2007

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Committee, I am Rear Admiral Steven K. Galson, Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency). Thank you for the opportunity to discuss FDA's role with regard to pharmacy compounding and compounded bio-identical hormone replacement therapies.

In my testimony, I will provide background information on pharmacy compounding, explain FDA's current statutory and regulatory authority in this area, and describe FDA's approach to address the public health issues associated with pharmacy compounding generally and compounded bio-identical hormone products in particular.

BACKGROUND

FDA's Historical Approach to Traditional Pharmacy Compounding

FDA believes that pharmacists engaging in traditional compounding provide a valuable medical service that is an important component of our pharmaceutical armamentarium. FDA regards traditional pharmacy compounding as the combining or altering of ingredients by a pharmacist in response to a licensed practitioner's prescription, which produces a medication tailored to an individual patient's special medical needs. In its simplest form, traditional compounding may involve reformulating a drug, for example by removing a dye or preservative in response to a patient allergy. Or it may involve making a suspension or suppository dosage form for a child or elderly patient who has difficulty swallowing a tablet.

It is FDA's view that compounded drugs are "new drugs" within the meaning of the Federal Food, Drug, and Cosmetic (FD&C) Act and that, like all new drugs, compounded drugs may not be introduced into interstate commerce without FDA approval. The drugs that pharmacists compound are rarely FDA-approved and they lack an FDA finding of safety and efficacy. However, as a matter of policy, FDA historically has not brought enforcement actions against pharmacists engaged in traditional compounding,

recognizing the important public health function that compounded drugs play for certain patients with specialized medical needs. Instead, FDA directs its enforcement resources against establishments whose activities raise the kinds of concerns normally associated with a drug manufacturer and whose compounding practices result in significant violations of the new drug, adulteration, or misbranding provisions of the FD&C Act.

FDA's Cooperation with States

FDA recognizes the important role of state authorities in overseeing the practice of pharmacy and generally defers to these authorities regarding the regulation of traditional pharmacy compounding. FDA often refers complaints to state authorities, provides them with support upon request, and cooperates with them in investigations and follow-on actions. However, state resources may be limited and states have varying standards and regulatory requirements that affect their oversight of pharmacy compounding. For example, it may be difficult for state regulators to respond to drugs that are compounded and shipped from across the country (or even from nearby states). Or state regulators may lack the resources or authority to respond to poor compounding practices in their own states. In cases like these, to protect the public health, FDA may need to act independently of state regulators.

FDA's Public Health Concerns Regarding Compounding

The public health threat posed by inappropriate drug compounding is the object of FDA concern and enforcement. Improper compounding has caused patient harm and death. Although many pharmacists are well-trained and well-equipped to compound certain medications safely, not all pharmacists have the same level of skills and equipment, and some products may be inappropriate for compounding. In some cases, compounders may lack sufficient controls (equipment, training, testing, or facilities) to ensure product quality or to compound complex products such as sterile or modified release drugs. The quality of the drugs that these pharmacists compound is uncertain and these drugs pose potential risks to the patients who take them.

Moreover, when compounding occurs on a large scale and it is not performed properly, compounders can expose many patients to health risks associated with unsafe or ineffective drugs. This is especially the case when patients take these compounded drugs in lieu of FDA-approved products.

FDA is also troubled by pharmacists that compound large volumes of drugs that are copies of FDA-approved drugs. This practice circumvents important public health requirements, including the FD&C Act's drug approval provisions. By definition, pharmacy compounding involves making a new drug whose safety and efficacy have not been demonstrated with the kind of data that FDA requires to approve a new drug. Consumers and health professionals rely on this evidence-based drug approval process to ensure that drugs are safe and effective.

FDA'S LEGAL AUTHORITY OVER COMPOUNDED DRUGS

The Federal Food, Drug, and Cosmetic Act

The FD&C Act's comprehensive scheme for the regulation of drugs includes provisions applicable to compounded drugs. Under the FD&C Act, it is unlawful to introduce or deliver for introduction into interstate commerce any new drug intended for human use without FDA approval. Title 21, United States Code (U.S.C.) §§331(d), 355(a). The FD&C Act defines a "new drug" as "*[a]ny* drug . . . that . . . is not generally recognized . . . as safe and effective for use under the conditions prescribed, recommended, or suggested in [its] labeling." *Id*. at §321(p). FDA has consistently interpreted the FD&C Act's broad new drug definition to embrace compounded drugs.

The FD&C Act also imposes requirements on drugs to ensure that they are not "adulterated," 21 U.S.C. §351, and it requires the labeling of drugs to provide consumers, physicians, and pharmacists with necessary information about drug contents, uses, and effects; drugs that are not properly labeled are "misbranded." *Id*. §352. The adulteration and misbranding provisions of the FD&C Act do not contain exemptions for compounded drugs.

To facilitate enforcement of the approval, adulteration, misbranding, and other FD&C Act provisions, Congress has authorized FDA to enter "any . . . establishment" where drugs are "manufactured, processed, packed, or held" and to inspect such establishments and "all pertinent equipment, finished and unfinished materials, containers, and labeling therein." *Id*. §374(a)(1). This authority extends to "all things" in these establishments, including records relating to prescription drugs. *Id.* The statute provides an exemption from records inspection for pharmacies that comply with local pharmacy law and that satisfy other criteria. But there is no specific exemption from inspection for compounding pharmacies or compounded drugs.

The 1992 Compliance Policy Guide on Compounding

FDA has long interpreted the FD&C Act to apply to compounded drugs, including the provisions addressing new drug approval requirements, adulteration, and misbranding. However, FDA has historically exercised its discretion to exempt from enforcement pharmacists engaged in traditional compounding.

In March 1992, responding to a significant increase in pharmacy compounding, FDA issued a compliance policy guide (CPG), section 7132.16 (later renumbered as 460.200) to delineate FDA's enforcement policy on pharmacy compounding. This CPG relied on enforcement discretion, rather than legal exemptions from the FD&C Act's new drug approval and other requirements, to guide FDA's regulatory approach. After Congress enacted the Food and Drug Administration Modernization Act of 1997 to specifically address FDA's role in the regulation of pharmacy compounding, the 1992 CPG was rescinded.

Food and Drug Administration Modernization Act of 1997

The Food and Drug Administration Modernization Act added section 503A to the FD&C Act to clarify the status of pharmacy compounding and compounded drugs under Federal law. Under section 503A, compounded drugs that satisfied certain requirements were exempted from three key provisions of the FD&C Act: (1) the adulteration provision of

section 501(a)(2)(B) (concerning good manufacturing practice requirements for drugs); (2) the misbranding provision of section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and (3) the new drug approval provision of section 505.

Thompson v. Western States Medical Center

Section 503A included prohibitions on the solicitation of prescriptions for, and the advertising of, compounded drugs. In November 1998, these solicitation and advertising provisions were challenged by seven compounding pharmacies as an impermissible regulation of commercial speech. A federal district court ruled in the pharmacies' favor and held that the solicitation and advertising restrictions violated the First Amendment. On appeal, the Ninth Circuit Court of Appeals affirmed the District Court's holding that the solicitation and advertising provisions unconstitutionally restricted commercial speech. The Court also declared section 503A to be invalid in its entirety, meaning that the unconstitutional speech provisions could not be severed from the rest of 503A. *Western States Medical Center v. Shalala*, 238 F.3rd 1090 (9th Cir. 2001)). The Supreme Court affirmed the Ninth Circuit's decision that the advertising and soliciting restrictions were unconstitutional, 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). FDA shares the Ninth Circuit's view that section 503A is now void.

Compliance Policy Guide of May 2002

In order to fill the regulatory vacuum created by the Supreme Court's decision in *Thompson v. Western States Medical Center*, FDA issued Compliance Policy Guide section 460.200 ["Pharmacy Compounding"] in May 2002. FDA issued this CPG in final form, and requested and received numerous comments on it. FDA stated that it would review these comments and revise the CPG, if appropriate. That process is underway, and FDA plans to issue a revised CPG, in draft, for public comment.

The 2002 CPG reflects FDA's current enforcement policy with respect to human drug compounding. It recognizes that pharmacists traditionally have extemporaneously compounded reasonable quantities of drugs upon receipt of a valid prescription for an

individually identified patient. This traditional compounding is not the subject of the guidance. Instead, the CPG provides that, when the scope and nature of a pharmacy's activity raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the FD&C Act, FDA will consider enforcement action. The CPG identifies factors that FDA evaluates in deciding whether to take action; these factors are not intended to be exhaustive.

Medical Center Pharmacy v. Gonzales

In 2004, ten pharmacies specializing in compounding brought suit in the United States District Court for the Western District of Texas, challenging FDA's authority to regulate compounded drugs. In August 2006, the court ruled, among other things, that compounded drugs are "implicitly exempt" from the FD&C Act's new drug approval provisions. *Medical Center Pharmacy v. Gonzales*, 451 F. Supp. 2d 854 (W.D. Tex. 2006). The government has filed an appeal with the U.S. Court of Appeals for the Fifth Circuit. Pending resolution of this appeal, the district court's decision applies in the Western District of Texas. Elsewhere, FDA continues to be guided by the 2002 CPG when considering enforcement actions regarding compounded drugs.

COMPOUNDED BIO-IDENTICAL HORMONE REPLACEMENT THERAPY PRODUCTS

FDA is aware that an increasing number of pharmacists compound hormone products for use by postmenopausal women. These pharmacies often promote their products as "bio-identical" to the hormones produced by a woman's body, and the phrase "bio-identical hormone replacement therapy" (BHRT) has been used to describe these products. Compounded BHRT products typically contain various forms of estrogen and progesterone and, in some cases, testosterone and dehydroepiandrosterone. BHRT drugs are compounded for oral, topical, transdermal, suppository, and other routes of administration.

FDA's regulatory approach toward compounded BHRT products is framed by its general approach to compounded drugs: FDA recognizes the legitimacy of traditional pharmacy compounding of BHRT products, *i.e.*, when a pharmacist compounds a BHRT product in response to a licensed practitioner's decision that a patient's specific medical need cannot be met by an FDA-approved drug. FDA will generally continue to defer to state regulators regarding this practice.

Claims Regarding Compounded BHRT Products

FDA is concerned, however, that a number of pharmacies make claims about compounded BHRT products that are false and that may mislead patients and practitioners as they decide whether these products are appropriate. Drugs that make false and misleading claims are misbranded under the FD&C Act.

FDA believes that some promotional materials for compounded BHRT products contain inaccurate information and do not adequately advise patients and practitioners of the risks associated with compounded hormone products (risks that appear to be the same as the hazards related to FDA-approved hormone products). These promotional materials may also contain unsubstantiated claims about the safety and efficacy of compounded BHRT products.

Moreover, some compounding pharmacists claim that their BHRT products are a "natural" alternative to FDA-approved drugs, because the compounded hormones are identical to the hormones produced in the body. These pharmacists may further claim that their "natural" compounded BHRT products are a safe alternative to FDA-approved drugs because they lack the risks and side effects associated with those drugs. FDA is unaware of any credible scientific evidence supporting the assertions that these bio-identical compounded products are a safe or effective alternative to FDA-approved drugs containing hormones.

Equally concerning are claims by compounding pharmacists that compounded BHRT products can be used to prevent serious illnesses, including breast and colon cancers, cardiovascular disease, and Alzheimer's disease. These claims are not substantiated by

scientific evidence for these compounded BHRT products, and they risk misleading consumers into using compounded BHRT products to prevent these illnesses in the absence of any evidence supporting there effectiveness.

FDA is also not aware of sound evidence showing the superiority of compounded BHRT products over FDA-approved drugs. Likewise, FDA has no information indicating that the side effects and risks of compounded BHRT products are dissimilar to those of FDA-approved drugs. Thus, claims regarding the safety, efficacy, and superiority of compounded BHRT products have not been substantiated by FDA and may mislead patients and practitioners.

Lack of Warnings and Information: Compounded BHRT Products

FDA regulations require prescription drugs containing estrogen to be dispensed with a patient package insert explaining the drug's benefits and risks. 21 CFR §310.515. Compounded BHRT products are often dispensed without this information. Thus, patients are not explicitly advised of the risks associated with the use of these compounded products. The absence of warnings and risk information may be viewed by patients as implicit evidence that compounded BHRT products are safer than FDA-approved drugs, when there is no data to support this conclusion.

FDA's Shared Concerns with Medical Professional Organizations

FDA is not alone in its concerns regarding compounded BHRT products. A number of medical professional organizations, including the American Medical Association (AMA), the Endocrine Society, and the American College of Obstetricians and Gynecologists have published formal statements regarding compounded BHRT products.[1] On the whole, these medical organizations believe that there is inadequate scientific evidence to support the claims made regarding the safety and efficacy of compounded BHRT products. Furthermore, two of these organizations, the AMA and the Endocrine Society,

[1] *See* American Medical Association House of Delegates Resolution 706, "FDA Oversight of Bio-identical Hormone (BH) Preparations," September 27, 2006; Endocrine Society Position Statement, "Bio-identical Hormones," October 2006; American College of Obstetricians and Gynecologists, Committee on Gynecologic Practice Opinion on Compounded Bio-identical Hormones, November 2005.

expressed concerns about the spread of false and misleading information in conjunction with the promotion of compounded BHRT products.

The Wyeth Citizen Petition

Currently, FDA is considering a Citizen Petition filed by Wyeth on October 6, 2005, concerning compounded bio-identical hormone replacement therapy drugs. FDA Docket No. 2005P-0411. The petition requests that FDA take a number of actions regarding compounded BHRT drugs, including enforcement action, investigations, requiring certain labeling and promotional disclosures, and engaging in educational initiatives. On April 4, 2006, Wyeth submitted a Supplemental Filing (Supplement) to the petition to address issues raised in comments submitted to the docket by the International Academy of Compounding Pharmacists and the National Community Pharmacists Association.

FDA has received more than 68,000 comments concerning this petition, and continues to receive comments. These include at least 13,000 form letters and comments from individual consumers, pharmacists, pharmacy groups, and health care practitioners. FDA also has received comments from consumer health care and professional organizations, including the National Women's Health Network, the National Black Women's Health Project, the National Association of Nurse Practitioners in Women's Health, the American Medical Women's Association, the North American Menopause Society, American Society for Reproductive Medicine, the Society for Women's Health Research, the Jacobs Institute of Women's Health, and the American College of Obstetricians and Gynecologists, among others.

The majority of the comments – submitted by individual consumers, health-care practitioners, pharmacists, alternative-medicine advocacy groups, and compounding pharmacy associations – ask that we deny Wyeth's petition. It is noteworthy, however, that we received some comments from pharmacists and health-care practitioners who are concerned about the use and marketing of compounded BHRT products. The comments received from consumer health organizations generally support Wyeth's petition.

The petition and comments raise complicated scientific issues of safety and efficacy, as well as regulatory and policy questions. FDA is currently evaluating these complex questions. When its analysis is complete, FDA will provide a written response to the petitioner, which will be available from FDA's Dockets Management Branch and will be posted on FDA's website.

Other Unapproved Hormone Replacement Products

FDA is concerned about the distribution of other unapproved hormone replacement products, including products marketed as over-the-counter drugs and dietary supplements.

In the fall of 2005, FDA worked with the Federal Trade Commission (FTC) on a joint effort to address the marketing of unapproved hormone replacement products. In November 2005, FDA sent warning letters to 16 dietary supplement and hormone cream marketers who were making unproven claims that their "alternative hormone replacement therapy" products were useful in treating or preventing cancer, heart disease, osteoporosis, and other serious diseases. All of the products were available for purchase directly from these firms' websites without a prescription. FDA advised the firms that their products were "new drugs" because they claimed that the products were useful in treating or preventing disease. The products were not approved by FDA for these uses, and thus violated the FD&C Act's new drug approval requirements. In addition, the firms violated an FDA regulation, 21 CFR §310.530, which prohibits the marketing of over-the-counter topically applied hormone-containing products without an FDA-approved application.

CDER issued three of the warning letters to these firms. Two of the three firms that received these letters no longer sell the hormone products. The third firm initially complied, but a recent review of the firm's website indicates that it is once again promoting hormone creams, albeit for different, less serious diseases. We are actively reviewing this matter to determine the best course of action.

The Center for Food Safety and Applied Nutrition (CFSAN) issued thirteen of the warning letters to firms marketing oral preparations as dietary supplements. Eleven of the thirteen firms that received these letters promised corrections that included removing the offending claims cited in the warning letters, discontinuing marketing the non-compliant products, or taking down the websites on which the products were marketed. CFSAN confirmed these corrections, but a recent review of the firms' websites showed that two firms are now marketing new products with similar claims. CFSAN is considering the steps that it will take to respond to this information.

FTC, in a joint effort with FDA, also sent notices to thirty-four websites promoting hormone replacement products with unsubstantiated claims. FTC stated in its "Notice of Potentially Illegal Marketing of Menopausal/Hormonal Products" that the FTC Act, 15 U.S.C. §41 *et seq.*, prohibits unfair or deceptive acts and practices, including false and unsubstantiated advertising claims.

FDA's Office of Women's Health (OWH) Menopause and Hormones Campaign

In FY 2003, OWH was mandated by Congress to spearhead an "Agency outreach campaign to provide concise information to women and health professionals about hormone replacement therapy" as a result of the findings of increased risk of heart attack, stroke and breast cancer in the National Institutes of Health (NIH) Women's Health Initiative (WHI) combination hormone therapy study in 2002. In this directive, FDA was to "work collaboratively with physicians, women's health groups, and federal agencies to conduct a public awareness campaign about the use of hormone therapy, including the treatment of menopausal symptoms."

The menopausal hormone therapy outreach campaign had two parts. Part I included the development of materials and partnerships (2003-2004) and Part II included nationwide media outreach (2004-2005).

Part I: Materials and Partnership development

OWH formed a working group that included members from CDER, HHS Office on Women's Health, NIH, Agency for Healthcare Research and Quality (AHRQ), and 25 women's health and health professional organizations. The group was tasked with identifying the target audience, developing key messages, campaign materials, and strategies for dissemination.

Rollout of the campaign materials was held on September 9, 2003. Materials included a fact sheet and a purse guide (discussed below). The targeted audiences were women ages 40-59, with a dissemination of materials to geographic areas across the U.S. with the greatest density of women in these age groups. The key messages, which were confirmed through focus group research, were:

- Menopause and Hormones: "What Can You Believe?"
- Get informed
- Talk to your health care professional and decide if hormone therapy is right for you.
- If you choose to use hormones, use them at the lowest effective dose for the shortest amount of time needed.

The "Menopause and Hormones" fact sheet defines menopause and symptoms, as well as hormone therapy for menopause. It also describes known benefits and risks of hormone therapy as well as advises:

- who should not take hormone therapy;
- that the risks and benefits may be the same for all hormone products; and
- that the risks and benefits of "herbs or other natural products" are not currently known.

The "Menopause and Hormone" purse guide contains questions to facilitate discussion between the woman and her health care professional on whether use of hormone therapy is appropriate. It also provides an area for taking notes, suggests other beneficial health tests or screening that could be discussed during the visit and provides federal resources to find more information on hormone therapy for menopause.

Part II: National media outreach

Campaign materials developed in Part I were publicized using several different approaches and elements to involve partners. These included FDA Public Affairs Specialists; media outreach in both print and radio; Internet advertising; print advertising; outreach to community based organizations; and direct e-mail.

Campaign Conclusions

Based on the combined circulation totals for all media activities used, projections of membership in the community organizations contacted, and volume of materials ordered, the campaign can account for nearly 100 million times that the menopause message was delivered to peri-menopausal and postmenopausal women. In addition, the materials developed as part of this Congressional mandate continue to be requested and distributed. These materials are free and can be accessed via FDA's Office of Women's Health website (*http://www.fda.gov/womens/menopause/mht-FS.html*) and the Federal Clearinghouse at Pueblo (*www.pueblo.gsa.gov*), and are available in both English and Spanish. An extension of this campaign involves the development of a brochure on FDA-approved medications for menopausal symptoms – which has become available in the past month. This document was created in response to requests from women for an FDA guide that provides basic information about menopausal hormone therapy and describes all prescription products currently approved by the Agency for this indication. The booklet is not intended to be used in place of the labeling, but to help women talk to their doctor, nurse, or pharmacist about what they should know about risks and side effects, and general safe use for each of these medications.

CONCLUSION

FDA intends to continue to address pharmacy compounding, including compounding of BHRT products, in a manner that respects traditional pharmacy compounding. FDA will pursue enforcement action against compounded drugs, including compounded BHRT drugs, when the compounding of these drugs raises concerns normally associated with

drug manufacturing and results in significant violations of the new drug, adulteration, or misbranding provisions of the FD&C Act.

This concludes my testimony, Mr. Chairman. I will be glad to answer any questions you may have.