Guest Editorial

Compound Fractures: The Battle Between Wyeth Pharmaceuticals and the Compounding Industry Over Bioidentical Hormones

This article first appeared, in slightly different form, in Integrative Medicine: A Clinical Journal. Oct/Nov 2006; 5 (5): 58-61 and is reprinted here with that journal’s permission.
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Bioidentical hormones are manufactured solely by compounding pharmacists. They are purported to have the exact molecular structure as endogenous hormones made in the human body and, in theory, produce the same physiological responses.

Compounding Basics

Drug compounding is a process by which a pharmacist or doctor combines, mixes, or alters ingredients to create a medication tailored to the needs of an individual patient. Until the advent of drug manufacturing in the 1950s, compounding was the exclusive method of preparing medications for clinical use. During the 1930s and 1940s, approximately 60% of all medications were compounded, compared to about one percent in 2006. The lack of interest in compounding by the emerging pharmaceutical industry was quite understandable, as it was found to be much more cost-effective to focus manufacturing energy on bulk production of the fewest number of individual combinations and standard dosages rather than attempt to meet the needs of large numbers of individual customers.

Today, compounding is typically used to prepare formulations that are not commercially available, such as medication for a patient who is allergic to an ingredient in a mass-produced product, liquid versions that are easier to swallow, flavored medicines for children, cream- or gel-based versions for topical application, medications discontinued by a manufacturer, or medicines of a different dosage or concentration than what is typically available. In-hospital compounding allows for formulation of intravenous antibiotic solutions, total parenteral nutrition units, and special pediatric dosages. Pharmacists may provide compounded drugs to patients only upon receipt of a valid prescription from a doctor or other medical practitioner licensed to prescribe medication. Many states specifically regulate compounding practices as part of their regulation of pharmacies, and some require that all licensed pharmacies offer compounding services.

Upwards of two million women in the US use such hormones on a daily basis for relief of symptoms associated with menopause and perimenopause. Both advocates of and companies involved in the manufacture and sale of compounded hormones claim such compounds are safer and more efficacious than synthetic prescription hormones sold by drug companies.

Synthetic hormones do not have the same chemical structure as endogenous hormones and may elicit different responses in the human body. Such potential variation in effect have been implicated, although without definitive proof, in the increased incidence of diseases reported in the 2002 Women’s Health Initiative (WHI), which linked the synthetic hormones Premarin™ and Prempro™ to elevated risk of stroke, breast cancer, heart attacks, and circulatory disease.

The growing industrial and legislative battle over synthetic vs. compounded hormones culminated in an October 2005 citizen’s petition to the Food and Drug Administration (FDA) filed by Madison, New Jersey-based Wyeth Pharmaceuticals, one of the world’s largest pharmaceutical and health care products companies. Wyeth requested the FDA to designate compounded bioidentical hormones as a “new drug,” subject to all FDA restrictions and requirements.
regarding the manufacture and sale of new drugs. A public, political, and medical maelstrom soon followed.

In Opposition

Both pharmaceutical companies and physician organizations have raised a variety of concerns over the past two decades regarding the formulation and distribution of compounded medications. Opponents of compounding voice concerns regarding maintenance of the quality, purity, potency, sterility, and stability of the original bulk ingredients used in compounding. Allegations have been made as to bulk pharmaceuticals being re-manufactured and tailored to an individual patient (such as preparing costly 5 mg tablets of an antihypertensive medication from one generic 20 mg pill). With specific regard to compounded hormones, pharmaceutical companies allege compounding pharmacies are essentially acting as drug manufacturers by mass-producing bioidentical hormones, which would violate federal law. Physician oversight on the industry is next to non-existent, as compounding is rarely, if ever, mentioned during conventional medical training, and most physicians reflexively expect products to be free from contamination and of uniform quality.

In 2003, the US General Accounting Office concluded: "While drug compounding is important and useful for patient care, problems that have occurred raise legitimate concerns about the quality and safety of compounded drugs and the oversight of pharmacies that compound them. However, the extent of problems related to compounding is unknown." Wyeth Pharmaceuticals, manufacturer of the synthetic hormone replacement therapy drugs Premarin and Premprio, suffered financially as a result of the 2001 WHI report. Sales of these drugs dropped significantly, with a 68% decline in sales of Premarin Family products between 2002 and 2004, plummeting from $1.3 billion to $880 million.

On October 6, 2005, Wyeth asked the FDA to investigate bioidentical hormone replacement therapy, stating that many compounding pharmacies were making unsubstantiated marketing claims that were confusing women about the risks and benefits of the hormones. In addition to casting doubt on safety and efficacy, they alleged that compounding pharmacies, not physicians, were dictating what patients should take and demanded that the FDA penalize compounding pharmacies via enforcement actions such as seizure of products, injunctions, and warning letters.

"As a pharmaceutical company, we’re highly regulated, and we’re sitting here watching people get prescriptions for things that aren’t adequately tested or that they aren’t being adequately warned about,” states Ginger Constantine, Wyeth vice president for women’s health care. "If the FDA takes a look and says, ‘We don’t see any problem here,’ then so be it, but we need to raise the issue.”

The pharmaceutical industry has powerful advocates in their corner. A number of respectable medical organizations, fearing that lack of federal oversight of the industry puts consumers at risk, filed amicus briefs to Wyeth’s citizen’s petition (an amicus brief is filed by an organization that is not a party to a particular lawsuit but is allowed to advise the court regarding a point of law directly concerning the lawsuit).

“The American Medical Women’s Association is concerned about the safety and purity of these unregulated compounds and about misleading claims related to the marketing of some of these...products,” wrote Linda Hallman, AMWA executive director, in a recent letter to the FDA supporting the Wyeth petition. “For these compounded products, there is no regulation of production, purity of product, and safety of dose, nor safety and efficacy studies.”

Perhaps the most politically credible ally of the pharmaceutical industry has been the American College of Obstetrics and Gynecology (ACOG). According to ACOG, most compounded products, including bioidentical hormones, have not undergone rigorous clinical testing for either safety or efficacy. Citing the lack of well-designed and well-conducted clinical trials of these compounded hormones, ACOG recommends that they should be considered to have the same safety issues as those synthetic hormone products approved by the FDA and may furthermore exhibit additional risks unique to the compounding process.

“There is no scientific evidence to support claims of increased efficacy or safety for individualized estrogen or progesterone regimens prepared by compounding pharmacies,” according to a Committee Opinion released by ACOG. “Furthermore, hormone therapy does not belong to a class of drugs with an indication for individualized dosing.”

In Support

In response to this political assault, a group of compounding pharmacies supported filed a lawsuit seeking protection from FDA incursion, stating that regulation of compounding pharmacies already falls under state law. They argued that compounding has been approved and regulated by state boards of pharmacy since the Food, Drug, and Cosmetic Act was passed in 1938, and that all ingredients are purchased from manufacturers or repackagers who must be FDA-registered and meet FDA specifications for safety and purity. The plaintiffs pointed out that, as with all pharmacists, compounding pharmacists are regulated and licensed by state pharmacy boards in the same way states regulate and license doctors and other health care providers. They noted that compounding pharmacists do not write prescriptions, but only fill prescriptions written by health care providers. Finally, the pharmacists stated that the compounding of medications was in the best interest of the public, the protection of which is the mandate of the FDA.
compounding a drug may “not advertise or promote the compounding of any particular drug, class of drug, or type of drug.” In response, a coalition of licensed pharmacies specializing in compounding drugs sought to prohibit enforcement of the subsections of FDAMA dealing with such advertising and solicitation, arguing that these provisions violate the First Amendment’s guarantee of free speech. The United States District Court for the District of Nevada agreed with pharmacists, holding that the provisions do not meet the test for acceptable government regulation of commercial speech. The Court invalidated the relevant provisions, essentially severing this one restriction from FDAMA. (The District Court did not overrule a Federal legal decision — it overruled a Federal legislative law.)

The Federal government appealed to the Court of Appeals for the Ninth Circuit, which did agree that the provisions regarding advertisement and promotion were unconstitutional, but also found them not to be severable from the rest of FDAMA. The case went before the US Supreme Court, which affirmed the Ninth Circuit’s ruling and, as a result, the entire section — including separation of compounded drugs from “new drug” status — was invalidated. With the rejection of this section of FDAMA, there was again no definitive legislation clarifying the legal status of compounded medications with regards to FDA jurisdiction. Thus, the battle over “new drug” vs. “not new drug” began anew.

Through this loophole, Wyeth filed its citizen’s petition to the FDA in October of 2005, renewing its request in early April 2006. The agency has yet to respond to Wyeth’s request, other than saying it needs more time to review the issue. Meanwhile, the compounding industry undertook a grassroots effort both in pharmacies and on the Internet, urging women and doctors to write the FDA to protest Wyeth’s petition. The ensuing flood of more than 40,000 emails and letters over a six-month period of time underscored how emotional the issue had become, specifically for the thousands of menopausal women who utilize compounded bioidentical hormones.

Whatever the FDA finally decides with respect to the designation of compounded bioidentical hormones, there is little doubt that it will have dramatic implications for both the compounding industry and women’s health.

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4. Ibid.
8. Tommy G. Thompson v. Western States Medical Center. Case No. 01-344 (9th Cir 2002).

Twisting in the Wind

However, the late 1990s witnessed an interesting and relevant twist to the “new drug” vs. “not new drug” controversy. The Food and Drug Administration Modernization Act (FDAMA) of 1997, signed by President Bill Clinton, exempted compounded drugs from “new drug” requirements, provided they satisfy a number of restrictions. The most relevant constraint to the current controversy was that pharmacies, licensed pharmacists, or licensed physicians

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According to one amicus brief, “When manufactured products are not appropriate for a patient, the pharmacist’s efforts to help patients make the best use of their medication are thwarted unless compounding is an option. Without pharmacy compounding, there would be no medication to dispense, nor any medication therapy to optimize. Compounding enables pharmacists to contribute their medication knowledge and expertise to produce individualized medications that meet these needs and improve health outcomes.”

Legislative history seems to secure the compounding pharmacy’s position. In 2002, the Supreme Court of the United States wrote the following:

The Government has an important interest...in permitting the continuation of the practice of compounding so that patients with particular needs may obtain medications suited to those needs. And it would not make sense to require compounded drugs created to meet the unique needs of individual patients to undergo the testing required for the new drug approval process. Pharmacists do not make enough money from small-scale compounding to make safety and efficacy testing of their compounded drugs economically feasible, so requiring such testing would force pharmacists to stop providing compounded drugs.

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