

## **New Controversy Over Menopause Hormones: FDA Gets Flood of Protest On Petition to Regulate Some Alternative Treatments**

By Tara Parker-Pope

From The Wall Street Journal Online on *May 2, 2006*

An unusual petition before the Food and Drug Administration has triggered a huge outpouring of responses from women, doctors and pharmacists, protesting a bid to crack down on certain menopause hormones.

The flood of more than 40,000 emails and letters over the past six months underscores how emotional the issue of menopause hormones has become, and raises questions about the growing industry of small-scale drug mixers who are making hormone medications from scratch.

Pharmaceuticals giant Wyeth, the biggest seller of prescription menopause hormones, has asked the FDA to take action against makers of pharmacy-mixed -- or "compounded" hormones -- which it says aren't being adequately regulated. The company contends many compounders make false claims about the drugs' safety and fail to tell women about the risks associated with hormone use.

These compounded medications, which use custom doses of plant-based hormones, are regarded by many women as safer and more natural than the commercial hormones made by drug companies. The custom drugs are often called bio-identical hormones because they are chemically similar to a woman's natural hormones. They have surged in popularity since a government study four years ago raised questions about the health risks associated with traditional menopause hormones made by drug companies, including Wyeth.

The FDA has said that women should assume all estrogen and progestin drugs carry similar health risks. The agency has yet to respond to Wyeth's request, other than saying it needs more time to review the issue. Whatever the FDA decides, it will have dramatic implications for the compounding industry and women's health.

Compounding pharmacies have been a niche industry that serves an important function in the health-care system, preparing custom-mixed drugs for patients who for some reason can't use drugs manufactured by pharmaceutical companies. For instance, compounders might make a chewable tablet or dye-free version of a medicine for patients with special needs. Many patients with allergies to certain drug ingredients, or who want medications no longer manufactured on a large scale, say compounders provide treatments they just can't get anywhere else.

Now, the interest in customized hormones has transformed the compounding industry into a significant player in menopause treatment. The question being raised by Wyeth is whether the business has reached a scale that means many compounders are acting more like a drug manufacturer than a corner drugstore, and thus should be regulated by the FDA.

"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," says 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."

Nobody knows how much of the prescription hormone market now goes to compounders, but the size of the consumer reaction to the Wyeth complaint suggests that compounders are providing drugs to a large number of women. Sales of commercial prescription drugs have fallen by about half since 2002, when the first health risks were reported, to about \$2 billion in annual sales now, according to consultants IMS Health.

What is also clear from the comments received by the FDA, is that many women are convinced compounded hormones are safer and more effective than commercial hormones. The overwhelming majority of responses were in protest of Wyeth's petition, and were the result of a grassroots effort in pharmacies and on Web sites to urge women and doctors to write to the FDA. An FDA staff person said there is a backlog of comments to be posted to the agency's online docket and the final number may exceed 50,000.

"There is no public risk to health, since these hormones are merely replacing what was lost due to age, diet, or environment," reads one response on the FDA docket. "These are the exact hormones that should be in the body, not synthetics, so [they] are much easier absorbed and assimilated by the body than other manufactured products."

Pharmacy groups and doctors who prescribe compounded hormones accuse Wyeth, which makes the biggest-selling hormone drugs Prempro and Premarin, of trying to shut down its competition, and say the effort threatens the health of patients who rely on compounded drugs.

"There are millions of women's lives and health involved in this," says Steve Metcalf, owner of Metcalf Pharmacy in Brevard, N.C., and one of the firms cited in the Wyeth complaint. "To remove the option for ladies who choose it and doctors who prescribe it is unfair to the public."

One reason many compounders are concerned about the Wyeth action is the company's track record. In 1994 Wyeth filed a similar request urging the FDA to reject an application for a generic version of Premarin on the basis that it wasn't chemically identical to the branded drug. In 1997, the FDA ruled in Wyeth's favor, effectively squelching all generic competition to Premarin.

Whether the FDA has any say this time around is a matter of debate. The compounding industry operates in something of a regulatory vacuum. Pharmacy practices are regulated by state pharmacy boards, while the FDA has purview over the drug-making business. In recent years the FDA has focused its enforcement actions against pharmacies to those linked with tainted products, those selling drugs on a large scale or those involved in some type of fraud.

Before bioidentical drugs are prescribed, a doctor typically performs a saliva test, which measures a woman's natural hormone levels. The belief is that the saliva test allows a doctor to better determine what hormones are in short supply in a woman's body. They then can prescribe a customized hormone mix that they say will do a

better job relieving menopausal symptoms with fewer side effects than commercially prepared hormone drugs.

"All hormones aren't created equal," says Erika Schwartz, a New York physician who prescribes compounded hormones. "It's what kind of hormone supplementation you use and how you balance it that makes a difference. I've taken bioidentical hormones myself for 10 years."

Critics of the Wyeth complaint say an important point being ignored is that the pharmacies are only dispensing prescriptions written by doctors.

"The doctors are the ones asking us to provide the service -- it's not just us saying we'll make it and handing it out to anybody who wants it," says Derick Anderson, a compounding pharmacist in Brookline, Mass.

But the saliva tests and follow-up visits can get expensive. The initial doctor visit can range from \$200 to \$400, with follow-up visits, costing \$125 to \$250, needed about every three months until a woman's hormones are considered "stable." Lab work each visit can cost \$100 to \$400, while the hormones cost \$30 to \$100 monthly. Unlike with prescription hormones, many of the costs aren't typically covered by insurance.

Groups like the North American Menopause Society and the American College of Obstetricians and Gynecologists have said there is no evidence that compounded hormones are better or safer than commercial drugs. In addition, they have raised questions about whether compounded drugs have been adequately tested.

"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."

Some doctors also question the reliability of saliva testing, saying that a woman's hormone levels vary dramatically and there is no evidence that hormone levels detected in saliva tests have anything to do with a woman's symptoms.

In 2004, the medical journal *Menopause* reported on a review of bioidentical hormones that concluded saliva tests weren't a reliable way to determine a woman's hormone needs. The report concluded that compounded hormones are "potentially harmful," and lack "scientific underpinning." The paper's lead author, Lisa Boothby, affiliate clinical assistant professor at the Auburn University Harrison School of Pharmacy, says she has no financial relationships with any drug firms.

The fact that major medical groups are skeptical about bioidentical hormones hasn't dissuaded doctors from prescribing them or women from using them.

One woman wrote to the FDA that she has been taking bioidentical hormones for four years "with great results." "I feel I am protecting myself from cancer and God knows what else," she wrote.

