



## American Academy of Family Physicians

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Vice President  
Science and Education  
Norman B. Kahn, Jr., M.D.

December 5, 2005

Andrew von Eschenbach, MD  
Acting Commissioner of the Food and Drug Administration  
Office of the Commissioner  
U.S. Food and Drug Administration  
Department of Health and Human Services  
5600 Fishers Lane  
Rockville, MD 20857-0001

RE: Docket Number 2005P-0411

Dear Dr. Eschenbach:

It has been brought to the attention of the American Academy of Family Physicians (AAFP) that there are many issues surrounding bioidentical hormone replacement therapies. While the AAFP does not have a position or policy statement on this issue, we have reviewed the American College of Obstetricians and Gynecologists committee opinion No. 322 entitled, "Compounded Bioidentical Hormones," which was recently published in the *Journal of Obstetrics and Gynecology*. The AAFP recognizes the excellent work of the ACOG committee in the development of this opinion, which should be given attention in this matter.

Sincerely,

Norman B. Kahn Jr., MD  
Vice President  
Science and Education

NBK/dls/rc

Enclosure (1)

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# ACOG

Committee on  
Gynecologic Practice

# Committee Opinion



Number 322, November 2005

## Compounded Bioidentical Hormones

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

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Compounded bioidentical hormones.  
ACOG Committee Opinion No. 322.  
American College of Obstetricians and  
Gynecologists. *Obstet Gynecol* 2005;  
106:1139-40.

**ABSTRACT:** *Compounded bioidentical hormones are plant-derived hormones that are prepared, mixed, assembled, packaged, or labeled as a drug by a pharmacist and can be custom made for a patient according to a physician's specifications. Most compounded products have not undergone rigorous clinical testing for safety or efficacy, and issues regarding purity, potency, and quality are a concern. Compounded hormone products have the same safety issues as those associated with hormone therapy agents that are approved by the U.S. Food and Drug Administration and may have additional risks intrinsic to compounding. There is no scientific evidence to support claims of increased efficacy or safety for individualized estrogen or progesterone regimens.*

Compounded drugs are agents that are prepared, mixed, assembled, packaged, or labeled as a drug by a pharmacist. Unlike drugs that are approved by the U.S. Food and Drug Administration (FDA) to be manufactured and sold in standardized dosages, compounded medications often are custom made for a patient according to a physician's specifications. One category of compounded products is referred to as "bioidentical hormones"; however, there is confusion over what this term implies. *Bioidentical hormones* are plant-derived hormones that are biochemically similar or identical to those produced by the ovary or body.

The steroid hormones most commonly compounded include dehydroepiandrosterone, pregnenolone, testosterone, progesterone, estrone, estradiol, and estriol (1). Bioidentical hormones made by a compounding pharmacist from a health care provider's prescription are available in various routes of administration, including oral, sublingual, and percutaneous or as implants, injectables, and suppositories. Examples of compounded hormones include Biest and Triest preparations. The name Biest (biestrogen) commonly refers to an estrogen preparation based on a ratio of 20% estradiol and 80% estriol on a milligram-per-milligram basis. A similar preparation, Triest (triestrogen), usually contains a ratio of 10% estradiol, 10% estrone, and 80% estriol. It is important to note that these ratios are not based on each agent's estrogenic potency but on the milligram quantity of the different agents added together (2). Purchases of compounded hormones are not typically reimbursed by insurance companies.

Most compounded products have not undergone any rigorous clinical testing for either safety or efficacy, and issues of quality assurance regarding the purity, potency, and quality of compounded products are a concern. From June 2001 to December 2001, the FDA analyzed 29 product samples from 12 compounding pharmacies (3). The types of products varied, but examples include oral, injectable, pellet implants, and inhalation compounds such as hormonal products, steroids, and antibiotics. Although none of the compounded products failed identity testing, 10 of the 29 products (34%) failed one or more standard quality tests performed. Nine of the 10 failing products failed assay or potency tests, with all products failing potency testing demonstrating subpotent results; that is, the products analyzed contained less of the active ingredient than expected. In comparison with these results, the analytical testing failure rate for drug therapies approved by the FDA is less than 2%.

Although many advocates and compounders of bioidentical hormones recommend the use of salivary hormone level testing as a means of offering individualized therapy, hormone therapy does not belong to a class of drugs with an indication for individualized dosing. Individualized dosing is indicated when a narrow therapeutic window exists for a drug or a drug class. Such drugs include those with nonlinear pharmacokinetics, those that are renally eliminated as the active drug, some that are not metabolized during first pass through the liver, and those with clearly defined therapeutic and toxic concentrations based on large population pharmacokinetic studies of serum concentrations. Steroid hormones such as estrogen and progesterone do not meet these criteria and, thus, do not require individualized dosing.

There is no evidence that hormonal levels in saliva are biologically meaningful. Whereas saliva is an ultrafiltrate of the blood and in theory should be amenable to testing for "free" (unbound) concentrations of hormones, this has not proved to be the case (4). The problem with salivary testing and monitoring of free hormone levels is twofold: 1) there is no biologically meaningful relationship between salivary sex steroidal hormone concentrations and free serum hormone concentrations and 2) there is large within-patient variability in salivary hormone concentrations (5-9). Salivary hormone levels vary depending on diet, time of day of testing, the specific hormone being tested, and other variables (6, 7, 10-12).

Currently, the FDA requires manufacturers of products approved by the FDA that contain estrogen and progestogen to use class labeling (the black box warning) reflective of the findings of the Women's

Health Initiative. However, because compounded products are not approved by the FDA and have no official labeling (ie, a package insert), they are exempt from including the contraindications and warnings required by the FDA in class labeling for hormone therapy. Given the lack of well-designed and well-conducted clinical trials of these alternative therapies, compounded hormone products should be considered to have the same safety issues as those associated with hormone therapy agents that are approved by the FDA. They also may have additional risks intrinsic to compounding. There is no scientific evidence to support claims of increased efficacy or safety for individualized estrogen or progesterone regimens.

## References

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