February 8, 2018

Scott Gottlieb, MD
Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Gottlieb:

The North American Menopause Society (NAMS), the American College of Obstetricians and Gynecologists (ACOG), the National Association of Nurse Practitioners in Women’s Health (NPWH), and HealthyWomen are writing to call your attention to our concerns regarding the serious health and safety risks associated with the use of compounded “bioidentical” hormone drug products currently being marketed for the management of menopause and other symptoms. **We hereby urge the FDA to take prompt action to address this growing problem and place compounded bioidentical hormones on the ‘difficult to compound list.’**

**Compounded Bioidentical Hormone Therapy for Menopause is Common and Patients Are Confused About Their FDA Approval Status**

Up to 2.5 million women may be using **unapproved**, compounded menopausal hormone products that have not been shown to be safe, effective, or of consistent quality.\(^1\) Surveys\(^1,2,3\) show that between 10% and 50% of women believe that compounded bioidentical hormone therapy is FDA-approved and 76% of respondents are uncertain whether their therapy is FDA-approved.\(^1\)

- 1 to 2.5 million U.S. women 40 years or older are taking compounded menopausal hormone treatments (CMHT) annually\(^1\)
- 26 to 33 million prescriptions are filled annually for CMHT, representing one quarter to one third of the total sales of menopausal hormone treatments\(^1,2,3\) and $1.3 to $1.6 billion in annual sales\(^1,2\)

**Key Points**

- There are numerous FDA approved estrogen and progestogen (synthetic progestin and progesterone) products.
- There is limited rationale for the use of non-approved products except for documented medical issues such as allergies or need for a dose or formulation not available as an approved product.
- There are no randomized trials demonstrating efficacy or safety of compounded bioidentical hormone therapy for treating menopausal symptoms.
The contents, dose, quality, and sterility of these compounded products are not subject to adequate regulatory oversight.

When pharmacokinetic studies have been performed, unacceptable variability in bioavailability, bioactivity, potencies, and patterns of absorption of compounded estrogens and progesterone raise serious concerns of over or under-dosing with potential risk of cancer.

Compounded products are not required to include package inserts, label, or standard warnings that all approved estrogen and progestogen products are required to provide.

Compounded oral and topical estradiol, oral and topical progesterone, oral and topical progesterone with estradiol, intravaginal DHEA and bioidentical hormone pellets and testosterone pellets need to be included on the difficult to compound list.

**Use of Hormone Therapy for Menopausal Women**

Many postmenopausal women have been prescribed systemic HT to relieve bothersome symptoms of menopause, including hot flashes, night sweats, and sleep disturbances, and for the evidence-based prevention of osteoporosis and related fractures. More recent evaluations of the large randomized Women’s Health Initiative (WHI) Trial suggest that benefits exceed risk for women under age 60 and within 10 years of menopause. Furthermore, systemic or low dose therapies are used for the treatment of Genitourinary Syndrome of Menopause (GSM) including vulvovaginal atrophy and recurrent urinary tract infections. Estrogen is the primary hormone used to treat symptoms related to ovarian failure/removal resulting in loss of estrogen. Progestogen (synthetic progestins or micronized progesterone) is used with systemic estrogen to prevent endometrial neoplasia in women with an intact uterus. Unopposed estrogen is associated with a higher risk (2.1 to 5.7) of endometrial hyperplasia and adenocarcinoma. A progestogen is needed for at least 10 to 14 days per month to prevent these endometrial effects.

There are numerous FDA-approved estrogen and progestogen products available to treat menopausal symptoms (oral, transdermal, vaginal; single or combined). However, due to fear of “hormone therapy” generated by publication of the initial results of the WHI in 2002, the recent United States Preventive Services Task Force recommendation giving hormone therapy a “D” for prevention of chronic disease, many women are fearful of using FDA-approved hormone therapy and instead, believe the media-hyped myths that compounded hormone therapy is safer and more effective than FDA-approved. In addition, compounded hormone therapy does not have FDA-approved labeling accurately stating the risks and containing the precautions necessary to safely take these drugs.

Our concern is that misleading marketing puts millions of women at risk. These non FDA-approved compounded bioidentical hormone therapy products are not supported by efficacy data or published safety data to establish correct and safe dosing ranges or safety profiles. They are marketed without approved class labeling specifying potential risks and adverse effects (that the FDA requires for all approved hormone therapy products) and without dosing or adequate directions for use. Virtually none of the compounded menopausal hormone...
Compounded Bioidentical Hormone Therapy Has Variable and Unverifiable Potency and Quality Control

Compounding pharmacists do not have access to the same manufacturing processes needed to provide product quality testing consistent with FDA standards. Compounded products vary in what they actually contain compared to what was written on a prescription and the quality of the compounded products may be substandard in some cases. Concerns exist for over and under dosing of both the estrogen and the progesterone components of compounded hormone therapy.\textsuperscript{13} The FDA’s Division of Prescription Drug Compliance and Surveillance evaluated 29 compounded drugs obtained from 12 compounding pharmacies.\textsuperscript{14} The agency reported that 10 of the products (34\%) failed one or more of their standard quality tests, including nine products (one of which was progesterone) that failed because they contained less of the active ingredient than indicated on the label. This compares to the less than 2\% analytical testing failure rate for commercially produced samples. The last sentence of the report: “\textit{The findings also highlight the importance of carefully and properly compounding drug products to minimize risks to consumers.}”\textsuperscript{14} A small (37/40 evaluable) randomized pharmacokinetic trial comparing compounded hormone therapy to approved therapy found “that the currently used doses of compounded hormones yield lower levels of estrogen (serum estradiol and estrone concentrations were lower than expected) compared to the standard-dose estradiol patch.”\textsuperscript{15}

Investigative reporting by \textit{MORE} magazine, which evaluated 12 prescriptions for TriEst, found that the potencies of estrogen and progesterone ranged from 67.5 to 268 percent of the amount specified on the labeling.\textsuperscript{16} Mahaguna reported that dosing of compounded progesterone vaginal suppositories did not match that of FDA approved vaginal gels, with only one of 10 tested within an acceptable potency range, and some formulations having abnormal pHs and elevated microbial counts.\textsuperscript{17}

Potential risks identified include that under-dosing the estrogen component might lead to an increased risk of bone loss, thus providing less protection against prevention of osteoporosis. Over-dosing the estrogen raises concern about the potential for increased risk of breast cancer. Under dosing the progesterone, particularly combined with over dosing estrogen could increase the risk of endometrial cancer. Progesterone combined with estrogen may be less likely to cause breast cancer, as was seen in a French E3N study, where the combination of estrogen-progesterone was associated with an RR of 1.00 (95\% CI = 0.83–1.22),\textsuperscript{18} but this finding cannot be extrapolated to non-studied compounded products where dosing is not accurately known.

\textbf{There is a Critical Need for Adequate Formulation, Absorption and Dosing of Progesterone to Prevent Endometrial Cancer}

Manufacturers of hormone therapies must conduct an endometrial safety trial of at least 12 months’ duration, many provide up to 24 months. The acceptable rate of hyperplasia is 1\% or less, with an upper limit of the confidence interval not exceeding 4\%. Progestogens which have received FDA approval for use in menopausal hormone therapies include synthetic progestins and more recently oral micronized progesterone.
Initially, progesterone was not used for menopause therapy because it was poorly absorbed and rapidly inactivated in the liver. However, micronization of progesterone produces adequate plasma and tissue levels when given orally.\(^{19}\) Micronized progesterone has been shown to protect the endometrium, however appropriate formulation and dosing are critical to achieve adequate absorption and efficacious effect on the endometrium, with little room for error. For example the PEPI trial showed endometrial protection when using 0.625 mg CEE plus 200 mg micronized progesterone daily compared with placebo.\(^{20}\)

In contrast two studies showed the risk when inadequate dosing or absorption occurs. The first, the European Prospective Investigation into Cancer and Nutrition found an increased risk of endometrial cancer in the estrogen plus micronized progesterone group with an elevated HR of 2.42 (95% CI 1.53-3.83), based on only 26 cases.\(^{21}\) Similarly, in the E3N\(^{22}\) (Etude Epidémiologique auprès de femmes de l'Education Nationale), a French cohort study from 1992-2008, a higher risk of endometrial cancer was observed with oral micronized progesterone (doses not available, available primarily as a powder leading to solubility and absorption concerns) when compared with never use. An elevated HR was found of 1.80 (95% confidence interval (CI): 1.38, 2.34), primarily with longer duration of use (≤5 years, HR = 1.39 (95% CI: 0.99, 1.97); >5 years, HR = 2.66 (95% CI: 1.87, 3.77)).\(^{22}\) This elevated risk of endometrial cancer is hypothesized as due to inadequate dosing/absorption of the progesterone.

Progesterone appears to be well absorbed when placed vaginally in approved therapies. An FDA approved vaginal gel (4%) dosed biweekly for 1 year with a 50 ug transdermal estradiol patch led to atrophic endometrium on biopsy in all subjects.\(^{23}\) Similarly, FDA approved progesterone capsules (100 mg) administered vaginally every other day given with a 50ug transdermal estradiol patch for 3 years led to atrophy on all endometrial biopsies.\(^{24}\) Concern, however, is raised that transdermal progesterone creams, such as those provided in compounded products, provide less endometrial protection.\(^{25,26}\)

**Cases of Endometrial Cancer with Compounded Hormone Therapy**

There is recently published evidence showing increased endometrial cancers resulting from the use of compounded estradiol and progesterone, both case series\(^{27}\) and survey data.\(^{3}\) Concern has been raised that these cases of endometrial cancer may be a result of inadequate transdermal absorption of compounded progesterone.\(^{3,25,26}\) An Australian case series\(^{27}\) described the development of endometrial cancer in three patients who developed endometrial cancer after using custom-compounded hormone therapy to relieve menopausal symptoms. The hormone therapy preparations included troches containing varying doses of estrone, estradiol, estriol, progesterone, and dehydroepiandrosterone, used for 2–4 years diagnosed with stage 1A or 1B, grade 2, endometrial cancer. The authors hypothesized that the development of endometrial neoplasm might have occurred if the estrogenic component of the troche was well absorbed, but the progesterone dose or absorption was inadequate. Without adequate manufacturing controls and clinical trials assessing endometrial safety with histologic evaluation of the endometrium by biopsy (as required for FDA-approved menopausal hormone therapy), women may receive excess estrogen with inadequate progesterone, thus risking endometrial hyperplasia or cancer.
Prior History of Compounded Bioidentical Hormones and the FDA (Not Reassuring)\textsuperscript{12,28}

- October 6, 2005—A citizen’s petition was submitted to FDA “to address issues related to the growing, unlawful manufacture and marketing of so-called “bioidentical” hormone therapy . . . are available from numerous compounding pharmacies throughout the United States.\textsuperscript{29,30,31}

- 2008—FDA granted the petition in part and denied it in part.\textsuperscript{30} The agency acknowledged that pharmacies providing compounded drugs should provide proper risk information and that compounded drugs are deemed to be misbranded if their labeling is false or misleading in any particular. The petition response stated that promotion for a compounded bioidentical hormone therapy (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.

- The agency agreed in the petition response to conduct a public awareness campaign that included releasing an article, published on FDA’s Consumer Health Information website page, titled “Bioidenticals: Sorting Myths from Facts,” issuing a press release, a Frequently Asked Questions (FAQs) document, and conducting telephone calls with the media and stakeholders to discuss the issues (all available on the website page).\textsuperscript{32}

Multiple Medical Organizations Have Expressed Concern about Risks with Use of Compounded Hormone Therapy

A scientific statement issued by the Endocrine Society in April 2016, stated: “The misconception that custom-compounded menopause hormone therapy (MHT) is safer, more efficacious, and less likely to cause cancer than FDA-approved MHT is not supported by any peer-reviewed publications or appropriately designed randomized controlled trials (RCTs).”\textsuperscript{33} The scientific statement goes on to say that there is “no rationale for routine prescribing of unregulated, untested, and potentially harmful custom compounded bioidentical hormone therapies.” The importance of physician and patient education about the differences and potential risks between approved products and less-regulated hormone formulations has become paramount to protect women from these risks if the state or government doesn’t take adequate action.

All of the major medical societies (including NAMS,\textsuperscript{4} ACOG,\textsuperscript{34} Endocrine Society,\textsuperscript{35} American Association of Clinical Endocrinologists,\textsuperscript{36} American Society for Reproductive Medicine,\textsuperscript{37} American Medical Association,\textsuperscript{38} The Women’s Health Practice and Research Network of the American College of Clinical Pharmacology,\textsuperscript{39} Nurse Practitioners in Women’s Health,\textsuperscript{40} International Menopause Society,\textsuperscript{41} Global Consensus\textsuperscript{42}) recommend against prescribing compounded hormone therapy to their members due to safety concerns that include minimal government regulation and monitoring, overdosing or under dosing, presence of impurities or lack of sterility, lack of scientific efficacy and safety data, and lack of a label outlining risks. There is a need for robust clinical studies to determine if there the benefits and risks of compounded bioidentical products compared with FDA approved and regulated manufactured products.\textsuperscript{4}
Although compounding pharmacies that are not outsourcing may voluntarily become accredited by professional groups such as the Pharmacy Compounding Accreditation Board (PCAB), the International Academy of Compounding Pharmacists, and Professional Compounding Centers of America, accreditation does not provide the same testing, regulation, approval process or monitoring that FDA approved products undergo.

**Misleading Advertising with Compounded Hormone Therapy**

There have been false and misleading advertising on the Internet and in other media outlets which promote these products, making claims of superiority and greater safety than approved products.\(^{43}\)

Examples of claims regarding compounded menopausal hormone therapy encountered on the Internet:

- Bioidentical hormones are “natural” and therefore safer with fewer to no side effects including a reduced risk of cancer
- Bioidentical hormones have more uses than FDA-approved menopausal hormone products (eg, Antiaging) and provide superior efficacy
- Compounding provides the ability to individualize therapy (customize) and more precisely identify dosing by use of salivary testing or repeated serum hormone determinations
- Salivary testing (offered by some of the compounding pharmacies) enhances individualization of therapy
- Many of the compounding pharmacies promote their skill and quality, which they state are necessary to provide compounded products with “good standards.”
- A number of large compounding pharmacies post “information for patients” on their website that review risks and benefits of hormone therapy that are not supported by evidence

**Difficult to Compound List**

The FDA is considering candidates for the list of drug products that may not be compounded because they have been found to be difficult to compound under sections 503A and 503B of the Food, Drug, and Cosmetic Act (21 U.S.C. 353a and 353b). To date, FDA has identified seventy-one unique drug products or categories of drug products that were nominated in response to FDA’s request for nominations for the list.\(^{44}\) FDA has conducted reviews of four categories of drugs (metered dose inhalers, dry powder inhalers, certain transdermal products and certain oral solid modified release drug products), and has presented the findings to the Pharmacy Compounding Advisory Committee (PCAC).

Oral and topical estradiol, oral and topical progesterone, oral and topical progesterone with estradiol, and bioidentical hormone pellets and testosterone pellets have been nominated for the difficult to compound list and intravaginal dehydroepiandrosterone (DHEA) is another candidate, likely to be added to the list. The nominated products meet the criteria for the list.
However, FDA has not yet provided the regulations necessary to create the difficult to compound list, nor has it indicated how it intends to prioritize its reviews of the remaining drugs and categories of drugs that were nominated for this list.

The risks associated with poorly formulated compounded hormone products are significant. NAMS and ACOG request that the agency make it a priority to promptly present these nominated products to the PCAC and move quickly to designate these products as difficult to compound under sections 503A and 503B.

We further request that FDA continue to address the false and misleading claims being made on the Internet and in other media outlets and educate healthcare providers about the risks associated with compounded hormone therapy products.

NAMS would appreciate the opportunity to meet in person to discuss solutions to this health risk for the millions of postmenopausal women being misinformed and inappropriately treated. Thank you for considering our request and attending to the health risks of the millions of postmenopausal women for whom we provide evidence-based healthcare.

Sincerely,

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References


