

Compounded “Bioidentical” Hormone Therapy

FDA Presentation

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Overview

Compounded Drugs and Their Use

- Drug compounding is often regarded as the process of combining, mixing, or altering a drug or its ingredients to create a sterile or non-sterile medication tailored to the needs of a patient.
- Compounded drugs can be important for patients whose medical needs cannot be met by an approved drug, such as for patients who:
 - Have an allergy to an ingredient of an approved drug
 - Cannot swallow a tablet or capsule and need a medicine in a liquid dosage form that is not otherwise available
- Compounded drugs are not reviewed by FDA for safety, efficacy, or manufacturing quality before marketing.
- Most compounders do not report adverse events to FDA.

Compounding Under Section 503A

- Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) describes the conditions under which drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, can qualify for exemptions from three sections of the FD&C Act:
 - FDA premarket approval requirements (section 505)
 - Current Good Manufacturing Practice (CGMP) requirements (section 501(a)(2)(B))
 - Labeling with adequate directions for use (section 502(f)(1))
- Generally, state boards of pharmacy have primary responsibility for the day-to-day oversight of state-licensed pharmacies that are not registered with FDA as outsourcing facilities. These compounders generally do not register with FDA.

Conditions of Section 503A Include:

- Drug is compounded for an identified individual patient based on the receipt of a valid prescription order
- If the drug is compounded from a bulk drug substance, it must:
 - be a component of an approved drug product, or
 - comply with the standards of an applicable USP or NF monograph and the USP chapter on pharmacy compounding, or
 - be on a list established by FDA.
- Compounders do not compound, regularly or in inordinate amounts, drug products that are “essentially copies” of a commercially available drug product.

Compounding Under Section 503B

- Section 503B of the FD&C Act describes the conditions under which drug products compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility can qualify for exemptions from three sections of the FD&C Act:
 - FDA premarket approval requirements (section 505)
 - Labeling with adequate directions for use (section 502(f)(1))
 - Drug supply chain security requirements (section 582)
- Outsourcing facilities are not exempt from CGMP requirements
- Outsourcing facilities must register with FDA and are subject to risk-based FDA inspections.

Conditions of Section 503B Include

- Outsourcing facilities may or may not receive prescriptions for identified individual patients.
- Drug is compounded in an outsourcing facility that does not compound using a bulk drug substance unless it appears on a list established by FDA of bulk drug substances for which there is a “clinical need” or unless the drug compounded appears on the drug shortage list
 - FDA is reviewing nominated bulk drug substances for the “503B bulks list”
- The compounded drug is not “essentially a copy” of one or more approved drugs

What are Compounded “Bioidentical” Hormones?

- Some compounded drug products containing reproductive steroid hormones are sold under the marketing term “bioidentical hormone therapy” (BHT).
 - marketed as identical (or highly similar) to endogenous human reproductive steroid hormones.
 - marketed as “natural” because the starting materials may be derived from biological sources such as plants.

Examples of Claims for Compounded BHT Products

- Certain healthcare practitioners prescribe and patients use compounded BHT instead of FDA-approved drug products
- Some BHT marketing claims that compounded BHT products are better than FDA-approved products because they:
 - are derived from natural sources
 - match hormones naturally occurring in the body
 - do not have the same risks or potential side-effects associated with FDA-approved products

Examples of Concerns Associated with BHT

- Compounded products, including BHT products, are not reviewed for safety, effectiveness, or quality before they are marketed.
- Statements made about compounded BHT may not have scientific support. Such statements may lead patients to take compounded BHT products instead of FDA-approved products in situations when the FDA-approved products would meet their medical needs.
- Compounded BHT products typically are not labeled with warnings that appear on FDA-approved drugs.
- Several women's health and medical organizations have expressed concern about the safety and clinical utility of BHT, both publicly and in direct outreach to FDA.

Examples of Concerns Associated with BHT

- During an inspection FDA found that one marketer collected more than 4,000 reports of adverse events in patients who were administered compounded BHT products over approximately four years. Adverse events identified include endometrial cancer, prostate cancer, stroke, heart attack, deep vein thrombosis, breast cancer, cellulitis, and pellet extrusions.
- FDA is aware of reports of virilization (e.g., baldness) in women who, after use of compounded BHT products, had significantly higher than normal serum testosterone levels.
 - Some aspects of female virilization, such as male pattern baldness, beard growth, and voice deepening, do not reverse when treatment is stopped and testosterone levels return to normal.

MedWatch Report

- 64-year-old woman had compounded testosterone pellets inserted by an “anti-aging medical doctor” to treat menopause symptoms
- Reported malaise, back pain, weight gain, acne, aggression, and hirsutism
- Fifty-two days after implantation, her total testosterone concentration was 299 ng/dL (reference range 2 to 45 ng/dL) and free testosterone concentration was 16 pg/mL (reference range: 0.2 to 5 pg/mL)
- Treated with alprazolam as needed.
- Six months later her serum testosterone had returned to normal levels.

MedWatch Reports

- 69-year-old man with a history of TIAs and coronary artery disease
- Compounded testosterone pellets inserted to “boost my T levels, to increase my metabolic burn rate, lose weight, reduce waist size, increase energy, and increase libido”
- Not advised of potential side effects
- Pre-implantation serum testosterone and PSA were normal; post implantation serum testosterone doubled and PSA elevated
- Had a myocardial infarction requiring 3 stents 10 weeks after implant
- Told by doctor who implanted pellets there was no connection and that risks are only with “synthetic testosterone”

Statement of Work

- Review the current and historic use of compounded BHT drug products to treat patients, including information about the medical condition(s) that these compounded drug products have been used to treat;
- Describe the physical and chemical characteristics of compounded BHT drug products (e.g., active ingredient, inactive ingredient(s), dosage forms, routes of administration, strengths);
- Review and assess the available evidence (or lack of evidence) regarding the safety and effectiveness of compounded BHT drug products;
- Based on the available evidence, summarize findings and make recommendations with respect to whether
 - there is clinical utility for compounded BHT drug products;
 - the available evidence of safety and effectiveness supports use of compounded BHT drug products to treat patients; and
 - there are patient populations that might need a compounded BHT drug product in lieu of an FDA-approved drug product.

Value of this Research

- Inform FDA's compounding work, including evaluation of which active ingredients may be used in compounding by outsourcing facilities.
- Inform healthcare providers' prescribing decisions and patients' choices about "bioidentical" hormone therapy.
- Inform consumers, professional societies as well as other federal agencies

Hormones for Review

Common Hormones in Compounded BHT Products – List for NASEM review

- ESTRIOL
- ESTRADIOL
- ESTRADIOL CYPIONATE
- ESTRONE
- PROGESTERONE
- PREGNENOLONE
- TESTOSTERONE
- TESTOSTERONE PROPIONATE
- TESTOSTERONE CYPIONATE
- DEHYDROEPIANDROSTERONE

Substances generally identified by information from inspections and investigations, as well as public sources, such as ACOG publications.

Not included are certain synthetic hormones we have seen used in compounded products that do not appear to be marketed as “bioidentical,” e.g., medroxyprogesterone acetate.

Six Hormones on the NASEM List Are in FDA-approved Drugs



Hormone / Hormone Derivative	Contained in FDA-Approved Drug?
ESTRIOL	NO
ESTRADIOL	YES
ESTRADIOL CYPIONATE	YES
ESTRONE	NO*
PROGESTERONE	YES
PREGNENOLONE	NO
TESTOSTERONE	YES
TESTOSTERONE PROPIONATE	NO*
TESTOSTERONE CYPIONATE	YES
DEHYDROEPIANDROSTERONE	YES

FDA will provide a separate spreadsheet with information on approved drugs that contain these ingredients

*Approved products containing testosterone propionate or estrone are on FDA's list of drug products that have been discontinued from marketing

Häggström M, Stannered, Hoffmeier et al. 2014. Diagram of the pathways of human steroidogenesis.
https://en.wikiversity.org/wiki/WikiJournal_of_Medicine/Diagram_of_the_pathways_of_human_steroidogenesis.
Last accessed in July 2017. WikiJournal of Medicine 1:5.

Examples of Compounded Hormone Products

- Examples of formulations from the Pharmacy Compounding Center of America
 - Estriol/Estradiol [80%/20%] 0.25 mg/Gm to 2.5 mg/Gm - Cream
 - Estriol/Estradiol [80%/20%] 0.25 mg/Gm to 2.5 mg/Gm/ and Progesterone 10 mg/Gm to 100 mg/Gm - Cream
- Examples of formulations from outsourcing facility product reports
 - ESTRADIOL .1 mg; PROGESTERONE 150 mg; TESTOSTERONE 2 mg; ESTRIOL .4 mg – Capsule
 - PROGESTERONE 300mg – Capsule
 - TESTOSTERONE 100 mg/1 g – Cream
 - ESTRIOL 3 mg/1 g – Cream
 - ESTRIOL 2 mg/1 g; ESTRADIOL 2 mg/1 g; PROGESTERONE 120 mg/1 g; TESTOSTERONE 4 mg/1 g – Cream
 - ESTRIOL 3 mg/1 mL; PRASTERONE 30 mg/1 mL; ESTRADIOL 1.2 mg/1 mL; PROGESTERONE 50 mg/1 mL; TESTOSTERONE 2 mg/1 mL - Gel
 - TESTOSTERONE PROPIONATE 20 mg/1 mL; TESTOSTERONE CYPIONATE 200 mg/1 mL – Injection, Solution
 - ESTRADIOL .3 mg/1 g; TESTOSTERONE .1 mg/1 g; - Ointment
 - TESTOSTERONE 100 mg/1 mg – Implantable Pellet
 - ESTRADIOL 18 mg/1 mg – Implantable Pellet
 - PROGESTERONE 25 mg; ESTRIOL 2.4 mg; ESTRADIOL .6 mg - Troche

Example of order form

Patient Allergies: _____

PRESCRIBER'S SIGNATURE: X _____ DATE: _____

Commonly Requested Compounds for Bioidentical Hormone Replacement Therapy

1. _____ **Bi-Est 50:50 (50% Estradiol - 50% Estriol) Cream (* 180-Day Exp.)**
 SIG: () 0.25mg () 0.5mg () 0.75mg () 1mg Frequency: _____
2. _____ **Bi-Est 80:20 (20% Estradiol – 80% Estriol) Cream (30-Day ONLY Exp.)**
 SIG: () _____mg Frequency: _____
3. _____ **Progesterone Cream**
 SIG: () 25mg () 50mg () 75mg () 100mg Frequency: _____
4. _____ **Progesterone Slow Release Capsule**
 SIG: () 50mg Capsule () 100mg Capsule () 200mg Capsule Frequency: _____
5. _____ **Progesterone Suppository**
 SIG: () 100 mg SIG: () 200 mg Frequency: _____
6. _____ **Testosterone Cream**
 SIG: () 0.5mg () 1mg () 2mg () 3mg Frequency: _____

FDA-approved Reproductive Hormones

- FDA has approved many brand and generic progestins, estrogens, and androgens for treatment of hormone deficits or other indications
- FDA-approved hormone products contain hormones that are chemically identical to endogenous human hormones and hormones that are synthetically modified
 - The hormones identical to endogenous hormones are: progesterone, estradiol, and testosterone
- FDA-approved hormone products are available in different routes of administration and formulations. Certain FDA-approved products contain multiple hormones (e.g., estrogen and progestin, with the progestin mitigating the estrogen-associated risks of endometrial hyperplasia/cancer)

Example: FDA-approved Products Containing Estradiol

- Different dosage forms
- Different routes of administration
- Range of doses
- Single active ingredient products and products that combine estradiol and progestins

Example: FDA-approved Products Containing Estradiol

Examples of dosage forms	Examples of dose ranges* for products with estradiol as the only active ingredient:
Oral tablets	0.5 mg, 1 mg, 2 mg
Transdermal systems, extended release	Range from 0.025 mg/24 hr to 0.1 mg/24 hr, with intermediate strengths
Transdermal gels and transdermal metered gels	0.25 mg to 1 mg
Transdermal sprays	1.53 mg/spray
Depot injectables with estradiol esters (cypionate, and valerate)	10-20 mg every 4 weeks (estradiol valerate)
Vaginal ring, creams, tablets	0.004 mg to 0.01 mg

*comparison of doses between different formulations is not recommended

Example: FDA-approved Products Containing Estradiol

Labeled Indications for FDA-approved Estradiol-only Products

- Treatment of vasomotor symptoms associated with menopause
- Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause
- Treatment of hypogonadism due to hypogonadism, castration or primary ovarian failure
- Prevention of postmenopausal osteoporosis
- Estradiol valerate by injection also has an additional indication: treatment of advanced androgen-dependent carcinoma of the prostate

Boxed Warnings for Approved Products Containing Estrogen

Boxed warnings include warnings related to:

- Endometrial cancer (when not used with progestin)
- Breast cancer (when used with progestin)
- Thromboembolic events (deep vein thromboses, stroke)
 - When used with progestin, warnings also include pulmonary embolism and myocardial infarction
- Dementia in women 65 years of age or older

Boxed warning recommends prescribing estrogens (with or without progestins) at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Considerations in Support of Research Goals

Understanding Use of Compounded BHT Products

Why do patients and providers use compounded BHT products in lieu of FDA-approved hormone therapy products?

What are the medical condition(s) that different types of compounded BHT drug products have been used to treat, and how do these compare to FDA-approved indications for hormone products?

- In general, FDA approves hormone products for indications in which there is well established evidence of efficacy
- Compounded BHT products are sometimes used for the same conditions that FDA-approved drugs treat, and sometimes used for different conditions

Physical and Chemical Characteristics

What are the different dosage forms, strengths, and ingredients used in BHT?

- Compounded BHT formulations are available in various routes of administration, including in oral, percutaneous, sublingual, implantable, and injectable forms.
 - Creams, capsules, and pellets appear to be the most common dosage forms for hormone products compounded by outsourcing facilities
- Common compounded BHT formulations include Biest (biestrogen) containing estradiol and estriol, and Triest (triestrogen) containing estradiol, estrone, and estriol.
 - https://www.medscape.com/viewarticle/571299_5
 - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3131235/>

Bioavailability Testing

- Bioavailability testing measures whether, how much, and how quickly active ingredient is absorbed from a drug product and becomes available at the site of action.
- Compounders do not routinely assess their products for bioavailability. Bioavailability of an active ingredient in a compounded product may be greater or less than in an FDA-approved product.
- Differences in dose, formulation and route of administration can affect a product's bioavailability, which in turn can affect its safety and/or efficacy.

Safety of Compounded BHT Products

What is the available scientific evidence on the safety of compounded BHT drug products and the strength of that evidence?

Do any of the reported safety risks associated with compounded BHT products depend on their characteristics (e.g., strength, dosage form)?

How does the available scientific evidence on the safety of compounded BHT drug products and strength of that evidence compare with that of FDA-approved drug products?

Are compounded BHT drug products associated with risks different from, or in addition to, those described in the labeling of comparable FDA-approved drug products?

- For example, class risks of estrogen products identified on FDA-approved labeling?

Safety of Compounded BHT Products

- Information related to safety may include:
 - Pharmacology, toxicology, pharmacokinetics, toxicokinetics, genotoxicity, developmental and reproductive toxicity, carcinogenicity
 - Adverse reactions reported in clinical trials, case reports, observational studies
 - Comparative data, if available, to FDA-approved products.

Effectiveness of Compounded BHT Products

What is the evidence of effectiveness, or lack of effectiveness of compounded BHT drug products for their intended uses and the strength of that evidence?

Does the effectiveness depend on the characteristics of the compounded BHT drug product (e.g., strength, route of administration, dosage form)?

How does the available evidence and strength of that evidence regarding compounded BHT drug products compare to that of FDA-approved drug products?

Examples of Safety and Effectiveness Considerations

- **Bioavailability of compounded BHT products, including the available scientific evidence about**
 - The testing for systemic exposure
 - Safety or effectiveness issues if bioavailability is unclear
- **Compounded drugs that contain more than one active ingredient, including the available scientific evidence that**
 - each component makes a contribution to the effectiveness or safety of the compounded BHT product
 - the dosing interval and dosage are appropriate for all components
 - potential interactions between ingredients are understood and do not have a deleterious effect

Examples of Safety Claims

- **What evidence, if any, supports safety claims made about compounded BHT products? Examples:**
 - BHT drugs containing hormones that are structurally similar to endogenous human hormones are safer/better than FDA-approved drugs
 - BHT drugs do not have the same risks or side-effects associated with FDA-approved drugs

Examples of Effectiveness Claims

- **What is the available evidence to support treatment claims of compounded BHT products that fall outside of the conditions that FDA-approved hormone products are indicated to treat?**

- Examples:

- Anti-aging
- Cardiovascular benefit
- Cholesterol reduction or treatment
- Alzheimer's Disease and memory loss
- Diabetes
- Depression
- Arthritis
- Head hair growth or increased head hair thickness
- Weight loss and weight control

Examples from: State of TN v. HRC Medical Centers, INC. Complaint

In Brief

- Compounded drugs can play an important role in patient care
- But compounded drugs should not be used if an approved drug is appropriate to meet a patient's medical needs
- For BHT products, we ask you to
 - Assess use
 - Assess extent of scientific evidence of safety and effectiveness
 - Assess clinical utility

Discussion and Questions



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