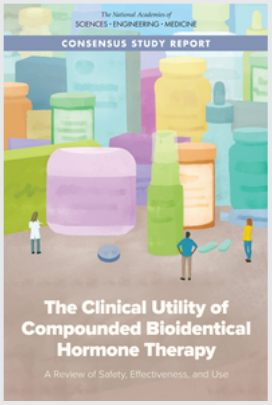

The Clinical Utility of Compounded Bioidentical Hormone Therapy: A Review of Safety, Effectiveness, and Use (2020)

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Donald R. Mattison, Ruth M. Parker, and Leigh Miles Jackson,
Editors

Committee on the Clinical Utility of Treating Patients with Compounded Bioidentical Hormone Replacement Therapy

Board on Health Sciences Policy

Health and Medicine Division

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COMMITTEE ON THE CLINICAL UTILITY OF TREATING PATIENTS WITH COMPOUNDED BIOIDENTICAL HORMONE REPLACEMENT THERAPY

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This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We thank the following individuals for their review of this report:

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report nor did they see the final draft before its release. The review of this report was overseen by **ELI Y. ADASHI,** Brown University, and **DAVID L. EATON,** University of Washington. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

Preface

Across the history of medicine, preparation of a compounded medication by a physician or pharmacist has been central to treating a variety of disorders. Historically, a compounded medication was formulated to treat an individual patient, and the science supporting the use of that compounded preparation was anecdotal. Over the past century, clinicians increasingly sought to improve and rely on the evidence of safety and effectiveness to support treatment decisions. During this same time, therapeutic data evolved away from information on a single patient treated with a medication specifically formulated to treat that individual patient to data that reflect how safe and effective the medication is for treating most patients with the disease.

This approach, leading to the development of U.S. Food and Drug Administration (FDA)-approved medications, and moving away from anecdotal evidence, decreased the demand for custom-compounded medications and substantially increased the use of medications tested and approved for treatment and prevention of specific diseases. More recently, over the past several decades, it has been observed that in certain instances, treatment needs to be individualized, producing a resurgence in the use of compounded medications. Treatment of menopause is one clinical area where the use of compounded bioidentical hormone therapy (cBHT) has been increasing. cBHT is marketed as a personalized and natural approach to enhanced wellness using tailored preparations that address a myriad of symptoms, including those associated with menopause and aging. The increase in supply and demand of cBHT has prompted the need for additional

data on the safety and effectiveness of these medications, as compounded medications are not reviewed for safety and efficacy or approved by FDA.

The Committee on the Clinical Utility of Treating Patients with Compounded Bioidentical Hormone Replacement Therapy was formed at the request of FDA to assess the clinical utility of cBHT. We, the members of this committee, began our work by defining clinical utility as a multidimensional construct that reflects evidence about safety, effectiveness, therapeutic need, and patient preference concerning benefit–risk balance. We then turned to explore existing evidence related to the attributes of cBHT from the perspective of clinical utility. We evaluated findings from a literature search of peer-reviewed evidence and gray literature (e.g., research reports, books for a lay audience) and held several open listening sessions to obtain input from various stakeholders. We heard presentations by researchers, clinicians, health advocates, representatives from government agencies, attorneys, and members of professional medical and pharmacy societies. In addition, we received extensive correspondence from stakeholders, including that of patients and providers who use cBHT, compounding (503A) pharmacists, and members of a coalition of (503B) pharmacists. In our deliberations, we worked to garner data for an evidence base relating to safety and effectiveness of cBHT, as these are two critical attributes of our definition of clinical utility.

In the course of the public meetings and based on the materials reviewed, the committee became even more aware of strong preferences for individualized treatment among certain individuals who use cBHT. As such, our work was guided by our collective commitment to keep patient autonomy as a core value. However, the committee also grappled with the concern that for the large patient population using cBHT, it is currently impossible for their clinicians to provide evidence-based guidance on the effectiveness or safety of each unique formulation. Therefore, the committee remained mindful that safety and effectiveness data are required for understanding risks and benefits for all therapeutics, and they are fundamental to how we practice medicine in this country. We thus worked to listen, collect, review, and assess the best available evidence regarding cBHT preparations in order to evaluate their clinical utility. We recognize that not all parties will be in agreement with this report's recommendations. Should further data from high-quality, well-controlled clinical trials become available, such evidence could be evaluated and the clinical utility of cBHT preparations could be reassessed. Our hope is that our findings, conclusions, and recommendations will inform patients, health care providers, and regulatory bodies to ensure patients have accessible and understandable information based on the best available evidence needed to support their decision making.

It was our responsibility and honor to chair this committee. Our efforts focused on evaluating cBHT within the context of current, FDA-approved

drugs, all of which have demonstrated clinical utility for treatment of symptoms of menopause. We want to thank our fellow committee members; without them, their perseverance, effort, and good humor, this consensus report would not have been possible. We also want to thank individuals who took time to come to the public sessions to share their experiences, insights, and compassion for those individuals seeking safe and effective treatment.

Our work could not have been accomplished without the concerted efforts of the committee members who did their work sensibly with cheerfulness and open minds. The committee's able and fearless staff, Andrew March, Elizabeth Townsend, Justin Jones, and led by the understanding and knowledge of Leigh Miles Jackson, could not have been more wonderful to work with or more essential to the committee's task.

Donald R. Mattison, *Chair*
Ruth M. Parker, *Vice Chair*
Committee on the Clinical Utility of Treating Patients with Compounded Bioidentical Hormone Replacement Therapy

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The committee takes this opportunity to recognize the many individuals and organizations who so generously gave their time and expertise to inform its work. To begin, the committee would like to thank the sponsor of this study, the U.S. Food and Drug Administration (FDA), for its guidance and support. The committee also greatly benefited from the discussions with individuals who attended and made public presentations (see Appendix A). The committee is thankful for the many contributions of these individuals.

The committee could not have done its work without the support and guidance provided by the National Academies project staff: Leigh Miles Jackson, study director; Elizabeth Townsend, associate program officer; Anna Sberegaeva, associate program officer; Andrew March, research associate; and Justin Jones, senior program assistant. We appreciate Victor Stewart for his financial assistance on this project, are indebted to Jennifer Hinners for her research and writing contributions, and gratefully acknowledge Carolyn Shore and Andrew Pope of the Board on Health Sciences Policy for the guidance they provided throughout this important study.

Many other staff within the National Academies provided support to this project in various ways. The committee would like to thank the executive office staff of the Health and Medicine Division, as well as Taryn Young and Bettina Seliber for the management of the report review and publication process. We would like to thank Jorge Mendoza-Torres and the National Academies Research Center staff for their assistance in the committee's research efforts, as well as the National Academies Press staff.

This committee is grateful to the research consultants that generously contributed to this body of work. We extend our thanks to Phebe Hong

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Finally, the committee is indebted to Joe Alper for his valuable commissioned work, and Mark Goodin for his editorial assistance in preparing this report.

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BOXES

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Acronyms and Abbreviations

ACCP	American College of Clinical Pharmacy
ACOG	American College of Obstetricians and Gynecologists
API	active pharmaceutical ingredient
BHRT	bioidentical hormone replacement therapy
BHT	bioidentical hormone therapy
cBHT	compounded bioidentical hormone therapy
CDC	Centers for Disease Control and Prevention
CGMP	current good manufacturing practice
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
CPG	Compliance Policy Guide
DHEA	dehydroepiandrosterone
DMF	Drug Master File
DQSA	Drug Quality and Security Act
E1	estrone
E2	estradiol
E3	estriol
FAERS	FDA Adverse Event Reporting System
FDA	U.S. Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act

FDCA	Federal Food, Drug, and Cosmetic Act
FSD	female sexual dysfunction
FTC	Federal Trade Commission
GABA	γ-amino butyric acid
HHS	U.S. Department of Health and Human Services
HSDD	hypoactive sexual desire disorder
IND	investigational new drug
LC-MS/MS	liquid chromatography–mass spectrometry
MFR	Master Formulation Record
MHT	menopausal hormone therapy
MOU	Memorandum of Understanding
NABP	National Association of Boards of Pharmacy
NAMSA	North American Menopause Society
NDA	new drug application
NECC	New England Compounding Center
NF	National Formulary
NHS2	Nurses' Health Study 2
PCAB	Pharmacy Compounding Accreditation Board
PCCA	Professional Compounding Centers of America
POI	primary ovarian insufficiency
PSA	prostate-specific antigen
RCT	randomized controlled trial
SERM	selective estrogen receptor modulator
USP	United States Pharmacopeia
USPSTF	U.S. Preventive Services Task Force
WHI	Women's Health Initiative

Summary

The U.S. Food and Drug Administration (FDA) has approved dozens of hormone therapy products for men and women, including estrogen, progesterone, testosterone, and related compounds. These products have been reviewed for safety and efficacy and are indicated for treatment of symptoms resulting from hormonal changes associated with menopause or other endocrine-based disorders.

In recent decades, an increasing number of health care providers and patients have turned to custom-formulated, or compounded, drug preparations as an alternative to FDA-approved drug products for hormone-related health concerns. These compounded hormone preparations are often marketed as "bioidentical" or "natural" and are commonly referred to as compounded bioidentical hormone therapy (cBHT).[1,2] In recent surveys, millions of men and women have reported using compounded hormone therapy, and today there is a broad array of compounded hormone

[1] As a consequence of cBHT marketing strategies, the term *bioidentical* is often misinterpreted by the general public. The committee intentionally includes the term when referencing certain types of hormone therapies, with the rationale that *bioidentical* serves as an important identifier for many compounded hormone therapies, and including the term may be a useful means of more effectively communicating the report conclusions to the general public. It should be noted, however, that the committee's use of the term *bioidentical* should not be interpreted as an endorsement.

[2] For the purposes of this report, *replacement* was removed from the term *BHT* to avert implications that the goal of hormone therapy is to replace hormone concentrations to the levels present in young adults. The official National Academies' language regarding the committee and its task still maintains the use of the original term.

formulations available for purchase, accounting for an estimated 26 to 33 million prescriptions that cost upwards of $2 billion annually. Media influences and targeted marketing approaches and claims have led many patients and certain prescribers to perceive cBHT preparations as safer and more effective alternatives to FDA-approved hormone products. Because compounded preparations are exempt from certain federal requirements for pharmaceuticals, these custom-compounded preparations are not required to demonstrate safety or effectiveness before they are dispensed to patients. In addition, many patients may believe that *bioidentical* hormone medications are only available through custom preparations at compounding pharmacies. However, FDA has approved several bioidentical hormone therapy (BHT) medications at different doses and with various routes of administration.

OVERVIEW OF COMPOUNDING

Compounding is the process of combining, mixing, or altering ingredients to create a medication tailored to the needs of a patient. Compounded drugs can provide therapeutic alternatives for patients with medical needs that cannot be met by available FDA-approved drug products. For example, compounding can provide customized formulations to (1) create alternate dosage strengths or forms or (2) omit components of FDA-approved drug products to which a patient has an allergy. Compounding can also fill gaps in cases where manufactured drugs are in short supply or have been discontinued. The process of compounding can produce sterile or nonsterile preparations, and it is conducted within a wide range of pharmaceutical and medical settings. Patient populations that have traditionally benefited from customized compounded formulations include pediatric patients, people living with chronic pain, people at the end of life, and people with certain specific medical conditions for which an FDA-approved drug product is not available.

Compounding can occur in community pharmacies, physicians' offices, and hospital pharmacies, collectively known as 503A compounding pharmacies. Traditionally, this practice of compounding was a small-scale, ad hoc, and patient-specific process, and the minimal regulations and oversight applied to the practice reflected that. However, recent years have seen an expanded supply and demand of compounded medications, as well as the emergence of large-scale compounding pharmacies that produce and sell greater volumes of compounded preparations in preset formulations, sometimes across state lines. This change in the compounding landscape prompted Congress to create a separate category of compounding facility—called an "503B outsourcing facility"—that is subject to an increased level of federal oversight, although not as strict as the FDA oversight for

manufactured products. (See below for an additional discussion of the inadequate regulation and oversight of compounding pharmacies and outsourcing facilities.)

CLINICAL UTILITY OF cBHT

In light of the fast-growing popularity of cBHT preparations, the clinical utility of these compounded preparations is a substantial public health concern for various stakeholders, including medical practitioners, patients, health advocacy organizations, and federal and state public health agencies. In fall 2018, FDA requested the National Academies of Sciences, Engineering, and Medicine (the National Academies) to appoint an ad hoc committee to examine the clinical utility of cBHT drug preparations, with a prioritized focus on preparations containing estradiol, estrone, estradiol cypionate, estriol, dehydroepiandrosterone (DHEA), pregnenolone, progesterone, testosterone, testosterone cypionate, and/or testosterone propionate. The resulting Committee on the Clinical Utility of Treating Patients with Compounded Bioidentical Hormone Replacement Therapy was charged with reviewing the uses of cBHT preparations and the available evidence that would support marketing claims of the safety and effectiveness of cBHT preparations.[3] The committee was also asked to assess whether the available evidence suggests that these preparations have clinical utility and safety profiles warranting their clinical use and to identify patient populations that might benefit from cBHT preparations in lieu of FDA-approved BHT.

Over the course of the study, the committee held nine meetings, five of which were information-gathering sessions open to the public. In addition to the evidence collected at its public meetings, the committee also conducted reviews of the peer-reviewed literature and gray literature (e.g., research reports, books for a lay audience) on topic areas relevant to the study's charge. In recognition of the limited information available addressing the use, safety, effectiveness, and patient perspectives of cBHT, the committee also made concerted efforts to collect and review relevant anecdotal, survey, and when possible, quantitative data from national stakeholders to supplement their research efforts. For example, relevant data was submitted by the following: FDA; Professional Compounding Centers of America; National

[3] While the terms *effectiveness* and *efficacy* are similar, they are not the same. The effectiveness of a drug refers to its therapeutic effect in real-world settings. The efficacy refers to the therapeutic effect in controlled clinical settings—such as phase 2 or phase 3 randomized clinical trials. This difference is critically important. Given the limited data on efficacy for cBHT preparations, the committee also considered clinical studies of effectiveness in its examination of clinical utility of cBHT preparations. Owing to its broader application to the body of research reviewed, the term *effectiveness* is used more generally across the report.

Association of Boards of Pharmacy; select state boards of pharmacy; a state attorney general's office; representatives of 503A compounding pharmacies and 503B outsourcing facilities; an editor-in-chief of a leading compounding journal; nonprofit medical and pharmacy societies and organizations; compounding advocacy organizations; nonprofit wellness organizations; women's health advocacy groups; and medical prescribers and researchers of cBHT. In addition, the committee reviewed submitted testimonies from thousands of patients who use cBHT.

CLINICAL UTILITY: SAFETY, EFFECTIVENESS, THERAPEUTIC NEED, AND USE OF cBHT

The primary focus of this report is on the term *clinical utility*. Clinical utility is a multidimensional, context-dependent term for which no standardized definition exists. However, based on review of the literature, including peer-reviewed articles, consumer surveys, and formal position statements and guidelines, the committee developed, for the purposes of this report, its own definition of the term. Here, clinical utility is defined as a multidimensional construct that reflects evidence about safety, effectiveness, and therapeutic need.[4] Patient preference is also a component of clinical utility and reflects patients' individual decision making, based on variable acceptance of benefits and risks.

Clinical Utility of cBHT: Safety and Effectiveness

The committee assessed components of clinical utility, safety, and effectiveness of cBHT by examining peer-reviewed evidence relevant to the 10 prioritized steroid hormones evaluated for this study. The committee also reviewed the public health protections offered by the current federal and state-level oversight of compounded preparations, as well as the reported number, types, and severity of adverse events related to use.

From the hundreds of submitted patient and prescriber testimonies, the committee determined there are a vast number of anecdotal claims and patient reports on the safety and effectiveness of cBHT. On the other hand, in the committee's review of the available peer-reviewed evidence, the committee found a substantial dearth of safety and efficacy data, including little or no high-quality pharmacokinetic data to inform evidence-based conclusions on the safety and effectiveness of cBHT preparations. These custom formulations have little or no data documenting absorption, distribution, and metabolism in the body, raising concerns about their safety

[4] In the context of this report, *therapeutic need* relates to the treatment of menopausal and male hypogonadism symptoms.

and underscoring the uncertainty about the reproducibility of the intended physiological effects of cBHT preparations.

The committee also determined that while some observational studies report data on the safety and effectiveness of cBHT, there are few well-designed, double-blind, randomized, placebo-controlled trials. The vast majority of the relevant studies reviewed had severe methodological limitations, the most common being the lack of standardized measures (e.g., assessments of hormone level, randomizations, participant exclusion and inclusion criteria, reporting measures) and minimal details on participant-specific dosing regimens, formulations, and dosage forms of the treatment arms, and where relevant, control arms of the study. Studies that lack this detail limited the interpretation and generalizability of the study results, and hindered the committee's ability to draw meaningful conclusions about the safety and effectiveness of cBHT.

The committee recognizes that for the large patient population using cBHT, it is difficult, if not impossible, for clinicians to provide equal evidence-based guidance on the safety or effectiveness of each unique formulation. That being said, the safety and effectiveness data are still required for understanding risks and benefits for all therapeutics, and they are fundamental to the practice of medicine in this country. Given the lack of high-quality, well-controlled data, the committee could not draw definitive overall conclusions on the safety or effectiveness of cBHT preparations. There is, however, some evidence to suggest that estriol may be effective in treating certain menopausal-related symptoms, including vasomotor symptoms and vaginal atrophy; however, as with the other hormones reviewed, the data do not support the claims of superior safety or efficacy of cBHT preparations compared to FDA-approved BHT preparations.

Of critical importance, the lack of data should never be interpreted as a marker of safety and/or effectiveness (i.e., the absence of evidence of harm is not the same as the evidence of absence of harms). In general, the contraindications for cBHT are expected to be similar to those of FDA-approved hormone products of the same class.

Given the lack of high-quality clinical evidence to demonstrate safety and effectiveness, there is a public health concern regarding prescribing, compounding, dispensing, and use of cBHT. Current federal and state oversight of the formulation, marketing, dispensing, surveillance, and adverse event reporting of compounded preparations are insufficient to identify and then communicate the risks assumed by patients when using cBHT. For example, while nonprofit scientific organizations such as the United States Pharmacopeia (USP) have issued national standards and guidance for individuals who compound, there is limited or inconsistent oversight of procedures related to formulation, testing for safety and effectiveness, and dispensing of compounded medications. In part, this has led to a lack of

standardization of best practices for compounding and dispensing cBHT preparations, resulting in significant state-by-state and even pharmacy-by-pharmacy variability in the compounded medications and related health information dispensed to patients.

In addition, unlike for FDA-approved BHT products, 503A compounding pharmacies and 503B outsourcing facilities are not required by federal regulations to include comprehensive product labels, similar to those required for FDA-approved products, or standardized package inserts for compounded preparations. These exemptions provide opportunities for ambiguous instructions for use, incomplete listing of active and inactive ingredients, or an omission of potential contraindications, all of which creates the potential for patients and prescribers to be inadequately informed about possible safety concerns related to the use of these medications.

Clinical Utility of cBHT: Therapeutic Need

FDA-approved BHT products are primarily indicated to treat vasomotor symptoms and symptoms of vulvar and vaginal atrophy associated with menopause, and for men, to treat symptoms of male hypogonadism or testosterone deficiency. However, collected testimony from marketing claims and cBHT advocates assert that cBHT is effective and safe for treating a broad spectrum of indications outside of those for FDA-approved BHT products, including anti-aging concerns (e.g., longer, fuller hair and smoother skin), sexual health, joint pain, general chronic pain, insomnia, cardiovascular diseases, and various mental health disorders.

To examine the evidence base to support the indication claims for cBHT, the committee reviewed available clinical guidance and published position statements issued by professional medical associations and societies (e.g., American Medical Association, Endocrine Society, North American Menopause Society) and other evidence-based clinical resources. Overall, the clinical guidance expresses concerns regarding the quality, safety, and effectiveness of cBHT preparations and cautions against their use in lieu of FDA-approved BHT options.[5] The committee was also unable to identify

[5] It should be noted that medical associations, societies, and other relevant health organizations that issue clinical guidance are often supported, in part, by the pharmaceutical industry. Furthermore, many of the coauthors of the issued guidance conduct medical research that may be funded, in part, by the pharmaceutical industry. All aspects of the pharmaceutical ecosystem (including FDA-approved and compounded drugs) should be extremely mindful of the great responsibility entrusted to them by the public to disclose all conflicts of interest (real and perceived) and to uphold esteemed medical and scientific ethics, values, and standards. After considering the disclosed conflicts of interest for the authors of the clinical guidance reviewed in this report, the study committee had sufficient confidence to allow the guidance to serve as an important piece of evidence used to inform its report conclusions.

any specific life-threatening medical conditions that necessitated the use of cBHT preparations.

In its review of evidence, the committee was able to identify clinical guidance that acknowledges certain uniquely specific situations for which there may be potential use for cBHT preparations. These situations can be organized into three specific categories: the avoidance of select components in FDA-approved products (e.g., because of allergies), testosterone use in women to treat female sexual dysfunction, and gender dysphoria.

Avoidance of Select Components of FDA-Approved Products

Allergies to ingredients in FDA-approved BHT products are a reported rationale for patient use of cBHT preparations. Although mentioned in clinical guidance as a potential rationale for cBHT use, clarification on the specific allergies that occur in response to FDA-approved BHT products is extremely limited in the literature. A review of anecdotal testimonies suggests that potential intolerances to FDA-approved BHT products include sedative side effects, gastrointestinal issues, or skin sensitivities to transdermal patches.[6] However, FDA's product database includes a range of available FDA-approved BHT formulations to help circumvent these concerns, and, with few exceptions, would allow patients the flexibility to avoid ingredients that may serve as potential allergens or switch dosage forms (e.g., from an oral medication to a transdermal patch) while having the assurance of safety and efficacy afforded by the FDA approval and oversight processes.

Female Sexual Dysfunction and Gender Dysphoria

Patients with female sexual dysfunction (FSD) and gender dysphoria are two indications for which there are no FDA-approved BHT products.[7,8] Often, both indications are treated with off-label use of FDA-approved BHT products. The committee was unable to identify any clinical guidelines that recommend the use of compounded hormone treatments, of any hormone, to treat FSD (including hypoactive sexual desire disorder or female

[6] Anecdotally, a commonly discussed exception is when a potential patient with a peanut allergy would be in need of a single-agent progesterone product.

[7] Female sexual dysfunction (FSD) is a complex condition associated with diagnostic classifications including hypoactive sexual desire, sexual arousal disorder, orgasmic disorder, or sexual pain disorder.

[8] A *DSM-5* recognized diagnosis that is "a noticeable incongruence between the gender the patient believes they are, and what society perceives them to be" (see the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, 2013).

sexual interest/arousal disorder) or gender dysphoria, in lieu of off-label use of FDA-approved BHT products.

Clinical Utility of cBHT: Patient Preference

Patient preference is perhaps the most complex consideration in the committee's definition of clinical utility. As discussed above, clinical guidance suggests there may be some clinical utility of cBHT, in lieu of FDA-approved products, in limited, specific situations. And yet, the suggested volume, scope, and clinical rationales for use of cBHT do not align with the evidence-based clinical recommendations from the medical community, contributing to a growing concern that cBHT is prescribed for reasons outside of a demonstrated unique therapeutic need.

Informed primarily by anecdotal testimonies and a few qualitative studies, the committee examined the factors seeming to have the greatest influence on patient preference for cBHT preparations. Based on a limited number of studies, patients (largely women) taking cBHT are thought to be simultaneously "pushed away" from FDA-approved BHT and "pulled toward" cBHT by conflicting psychosocial forces. Specifically, the committee identified several factors that may influence preference for cBHT including the early analysis and science communication efforts related to the Women's Health Initiative study; FDA requirements for labeled indications and boxed warnings for certain FDA-approved BHT products; cBHT marketing; physician practices and perspectives; patient mistrust of the health care industry and commercial pharmaceutical industry; interest in the "natural" movement; and prescription costs.

The committee knows little about how patients are first introduced to cBHT as a treatment option; however, available sources suggest that many rely on media outlets (e.g., social media, books, television commercials) to educate themselves about cBHT. In addition, research uncovered that certain patient motivations, influenced by marketing strategies, "pulling" them toward cBHT were beliefs that cBHT was "natural," as well as safer than FDA-approved BHT, and that these motivations were often influenced by marketing strategies used by advocates and suppliers of compounded medications. Additionally, there is evidence that many physicians are uncertain about whether cBHT is or is not an FDA-approved product. This implies there are inadequacies in prescribers' continuing education efforts, as well as in science communication and health literacy. Given the inadequate labeling of compounded preparations, there are concerns about how well vital information regarding potential risks and benefits is communicated to patients and prescribers. In the absence of safety and effectiveness data of cBHT, aspects of patient preference should not be the sole driver for use.

THE CLINICAL UTILITY OF cBHT AND RELATED CONSIDERATIONS FOR PRESCRIBERS

Given the paucity of data on the safety and effectiveness of cBHT, the **committee concludes there is insufficient evidence to support the overall clinical utility of cBHT as treatment for menopause and male hypogonadism symptoms.** The committee determined there is substantial patient interest and apparent use of cBHT to treat menopause and male hypogonadism symptoms. The limited oversight and surveillance of the large amount of clinical use of cBHT, including when, why, and which cBHT preparations are prescribed, is a concern. Nonetheless, within the body of evidence reviewed, there are potentially a few specific medical circumstances for which there may be clinical utility of cBHT, such as for patients who have an allergy to specific ingredients in an FDA-approved drug product or patients that require a dosage form not currently available as an FDA-approved drug product. Should further data from high-quality, well-controlled clinical trials become available, such evidence could be evaluated and the clinical utility of cBHT preparations could be reassessed.

Considerations for Medical Practitioners and Providers

Acknowledging, on the one hand, the substantial interest in and use of cBHT, and on the other, a lack of evidence to support the clinical utility of cBHT, the committee recognizes important professional obligations for stakeholders (i.e., physicians who prescribe and pharmacists who compound and fill these prescriptions) to uphold. These obligations include respecting patient autonomy—meaning the right of patients to choose—while at the same time ensuring that patients' decision making is informed by the best available evidence and supported with shared decision making.

Based on the precautionary principle, medical practitioners prescribing hormone therapy have a duty to engage in practice informed by evidence-based clinical guidelines and to educate patients to ensure that their decision making is informed by evidence-based health information. Health literacy and its reliance on evidence is foundational to autonomous patient decision making, and patients must have ready access to the best available evidence that is easy to understand and use as they weigh the risks and benefits of therapeutic options. In consideration of these obligations, concerns arise from areas of potential liability for prescribers of cBHT, which may include the invalidation of malpractice insurance, personal liability, or possible criminal charges.

Pharmacists and other qualified compounders have a professional obligation to follow USP's recommended standards and protocols to ensure safe manufacturing and dispensing of all medications in order to minimize

safety concerns. They also have an obligation to provide clear directions for use, have a clear rationale for each ingredient used in the medication, as well as include evidence-based information about the medication's potential adverse effects.

RECOMMENDATIONS

There is a dearth of evidence to support many of the marketed claims for the clinical utility of cBHT as a treatment of menopausal and male hypogonadism symptoms. Based on its examination of its clinical utility, the committee recommends restricted use of cBHT, assessments of their difficulty to compound, and additional education, oversight, and research.

Recommendation 1: Restrict the use of compounded bioidentical hormone therapy (cBHT) preparations.
Prescribers should restrict the use of cBHT preparations to the following: documented allergy to an active pharmaceutical ingredient or excipient of U.S. Food and Drug Administration (FDA)-approved drug product, or a documented requirement for a different dosage form. Patient preference alone should not determine the use of cBHT preparations.

In general, the potency of cBHT doses should not exceed those of FDA-approved hormone therapy products because of potential safety concerns. Any use of cBHT, including therapy for gender dysphoria, should align with established clinical guidance and require documentation of shared decision making and rigorous monitoring for long-term risks.

Prescribers and compounding pharmacists should clearly explain the limited evidence-based information about the safety and effectiveness of cBHT preparations. They should inform patients that compounded preparations are not FDA approved.

Recommendation 2: Review select bioidentical hormone therapies and dosage forms as candidates for the U.S. Food and Drug Administration (FDA) Difficult to Compound List.
The Pharmacy Compounding Advisory Committee should review the following bioidentical hormone therapies as candidates for FDA's Difficult to Compound List: estradiol, estrone, estradiol cypionate, estriol, dehydroepiandrosterone, pregnenolone, progesterone, testosterone, testosterone cypionate, and testosterone propionate. These candidates have safety and efficacy concerns related to the lack of bioavailability data and product-to-product variability as a result of drug formulation differences, stability, and quality control.

The Pharmacy Compounding Advisory Committee should consider all compounded bioidentical hormone therapy preparations formulated in pellet dosage form as candidates for FDA's Difficult to Compound List.

Recommendation 3: Improve education for prescribers and pharmacists who market, prescribe, compound, and dispense compounded bioidentical hormone therapy (cBHT) preparations.
To ensure the appropriate clinical use of cBHT, the committee recommends the following for prescribers:

- State medical boards, the Federation of State Medical Boards, and medical professional societies and associations (e.g., American Medical Association [AMA], Endocrine Society, North American Menopause Society) should advocate for a state-level certification for individuals who are seeking to begin or continue to prescribe cBHT. Formal clinical education should be offered in parallel to continuing medical education courses.
- Nonprofit professional societies and organizations within the medical sectors (e.g., AMA) should expand and promote evidence-based guidelines and best practices for clinicians who prescribe or compound cBHT preparations. These guidelines should include not only evidence-based conclusions on the potential benefits and risks, but also practical steps of when to consider cBHT in lieu of U.S. Food and Drug Administration (FDA)-approved products, which potential formulations should be considered, and the contraindications associated with the treatment.

To ensure the appropriate clinical use of cBHT, the committee recommends the following for prescribers and pharmacists:

- State boards of pharmacies, National Association of Boards of Pharmacy, Pharmacy Compounding Accreditation Board, local and regional schools of pharmacies, and nonprofit professional societies and organizations within the medical and pharmaceutical sectors with a particular focus in epidemiology and women's health, (e.g., American Association of Colleges of Pharmacy, AMA, Endocrine Society, North American Menopause Society) should develop pathways to support and incentivize the attainment of more in-depth training on complex compounding of hormone preparations. These courses should do the following:
    - Be conducted by schools of pharmacies or nonprofit professional societies and organizations within the medical and pharmaceutical sectors.

  - Include a review of the compounding process, including complexities of formulation science.
  - Examine the current peer-reviewed, evidence-based conclusions on the safety and effectiveness of commonly prescribed cBHT preparations.
  - Review the potential risks and reported adverse effects associated with the use of cBHT and FDA-approved products with the same active ingredients.
  - Describe potential conflicts of interest that exist within the prescribing, compounding, and treatment sectors of pharmaceutics.
- Additional continuing medical education courses hosted by for-profit organizations should not substitute for this training.

Recommendation 4: Additional federal and state-level oversight should be implemented to better address public health and clinical concerns regarding the safety and effectiveness of compounded bioidentical hormone therapy (cBHT).

The National Association of Boards of Pharmacy (NABP) and state boards of pharmacy should expand and improve their oversight and review of 503A compounding pharmacies to ensure that adequate quality standards are maintained and documented for every cBHT preparation dispensed. This increased oversight should include the following:

- All 503A compounding pharmacies should provide a standardized insert for dispensed cBHT preparations. The insert should:
  - Include a detailed description of the preparation's formulation, including all active pharmaceutical ingredients and the excipient(s) used, and use of the established name of the drug.
  - Clearly note that the preparation has not been U.S. Food and Drug Administration (FDA) approved for use and that rigorous bioavailability data, such as that available on FDA-approved products, are not available.
  - Include indications and guidance for use (administration), dosage strength and form, statement of compliance to current good manufacturing practices or United States Pharmacopeia (USP) standards, beyond use date, contraindications, side effects, caution for potential adverse effects, and instructions on how to report adverse events.
  - Include information on the person responsible for the quality and safety of the dispensed cBHT preparation, such as the establishment's supervising pharmacist or other designated individual, and the name and contact information for the pharmacy.

- All cBHT preparations dispensed from 503A compounding pharmacies should include boxed warnings for potential adverse effects for compounded prescriptions that include estrogens (estradiol, estriol, estrone) and androgens (testosterone), like those used in FDA-approved drug products with boxed warnings to educate the user about potential health risks.
- All 503A compounding pharmacies should increase their surveillance capacity by monitoring, recording, and annually reporting the types, formulations, payer, and dispensing rates of cBHT preparations. Data on the volume and types of cBHT dispensed should be submitted annually to a central repository within NABP and made available for public access.
- All 503A compounding pharmacies should be required to monitor and report all adverse events of cBHT preparations to state boards of pharmacy and simultaneously to MedWatch and the FDA Adverse Event Reporting System. Annual adverse event reports for nonsevere and non-life-threatening events should also be submitted. These reports should include information on the frequency, type, and severity of adverse events related to the use of cBHT.
- All states should uniformly and immediately adopt USP <795> and <797> standards to ensure the quality of dispensed sterile and nonsterile cBHT preparations. USP <795> and <797> should be considered minimum standards, and regulators should apply additional standards where needed to reduce patient risk.

FDA should continue to incorporate public health considerations into its regulation of the manufacturing, testing, and dispensing of cBHT by 503B outsourcing facilities. These considerations should include:

- Expand the requirement for 503B outsourcing facilities to provide information on the bioavailability and effectiveness of common cBHT preparations (e.g., Bi-est, Tri-est, all sterile preparations including pellets), in addition to their current focus on quality, purity, and sterility.
- All 503B outsourcing facilities should use a standardized insert for dispensed cBHT preparations. In addition to the current requirements, the insert should include:
    - A detailed description of the preparation's formulation, including all active pharmaceutical ingredients and inactive ingredients (e.g., excipients) used.
    - Clearly note that the preparation has not been FDA approved for use, and that rigorous bioavailability data, such as that available on FDA-approved products, are not available.

  - Include indications and guidance for use (administration), dosage strength and form, statement of compliance to current good manufacturing practices or USP standards, beyond use date, contraindications, side effects, caution for potential adverse effects, and instructions on how to report adverse events.
- All cBHT supplied by 503B outsourcing facilities should include boxed warnings for potential adverse effects for compounded prescriptions that include estrogens (estradiol, estriol, estrone) and androgens (testosterone), like those used in FDA-approved drug products with boxed warnings to educate the user about potential health risks.
- Modify the standard MedWatch form to adequately collect and track adverse events data related to cBHT use, including but not limited to:
  - All active pharmaceutical ingredients and excipients in the cBHT formulation.
  - Potential drug–drug interactions.

Recommendation 5: Collect and disclose conflicts of interest.
Prescribers and compounders of compounded bioidentical hormone therapy (cBHT) may have conflicts of interest arising from financial relationships (e.g., ownership or investment interests held in specific cBHT formulations or companies), and such conflicts should be transparent, publicly available, and disclosed to patients at the point of care. In addition, state licensing boards should collect and archive information on such financial relationships in a publicly accessible repository.

Recommendation 6: Strengthen and expand the evidence base on the safety, effectiveness, and use of compounded bioidentical hormone therapy (cBHT) preparations.
As the field of personalized medicine continues to expand, interest in compounded medication is likely to grow. Ensuring the safe and appropriate dosing of cBHT formulations requires the evaluation of the bioavailability of all active ingredients included in the preparation.

To develop a comprehensive evidence base on the potential health benefits and risks of specific cBHT preparations, public agencies (e.g., National Institutes of Health) and philanthropic funding agencies should establish, provide, or increase funding for clinical, epidemiologic, and health services research to address gaps in the evidence base.

Other stakeholders, including the U.S. Food and Drug Administration (FDA), the United States Pharmacopeia, 503A compounding pharmacies

and 503B outsourcing facilities, state medical boards, state boards of pharmacy, nonprofit professional societies and organizations within the medical and pharmaceutical sectors, pharmaceutical industries, and clinical and public health research groups should advocate for and support these research initiatives. Stakeholders should also develop a strategic plan to support precompetitive research projects and activities.

Prioritized research objectives should include, but not be limited to, the following:

- Data collection and surveillance.
  - Accurate and consistent collection of adverse event data for each cBHT preparation, by formulation and compounder.
  - Accurate determination of volume, scope, and financial costs of prescribed cBHT preparations in the United States.
- Clinical research on safety and efficacy.
  - Conduct additional well-controlled trials (with or without active comparators) for commonly prescribed cBHT preparations and dosage forms, including formulations that include estrone, estradiol, estriol, progesterone, or testosterone, to examine effects on safety and symptoms associated with perimenopause and menopause.
  - Generate bioavailability data for all active ingredients in the most commonly prescribed cBHT preparations to inform safe and effective dosing practices. Studies that include FDA-approved hormone therapy products with comparable active ingredients and dosage forms may help to inform clinical practice.
  - Develop observational studies of genetic and lifestyle variation (smoking, alcohol, diet) in cBHT responses, including adverse events.

All clinical trials or observational studies related to the safety, effectiveness, and use of cBHT should register with and be approved by an appropriate institutional review board, as well as obtain informed consent from all patients and study participants.

1

Introduction

The U.S. Food and Drug Administration (FDA) has approved dozens of hormone therapy products for men and women, including estrogen, progesterone, testosterone, and related compounds (FDA, 2019). These products are approved to, among other things, address hormonal changes associated with aging or other endocrine-based health concerns (ASA, 2006; de Villiers et al., 2016; Stuenkel et al., 2015). By the end of the twentieth century, hormone therapy became one of the most prescribed drug treatments for women in the United States (Brett and Burt, 2001).

In response to the growing popularity of hormone therapy, the National Institutes of Health in the 1990s launched the Women's Health Initiative (WHI), a comprehensive, prospective study, to test whether hormone therapy would prevent heart disease and to examine overall health risks and benefits of FDA-approved hormone therapy (Hays et al., 2003; Stefanick et al., 2003). In the years since, researchers have published more than 100 findings related to a broad spectrum of health risks and benefits associated with the use of hormone therapy in postmenopausal women (WHI, 2020). Early analysis and science communication efforts for WHI, coupled with FDA's limited indications for use of hormone therapy and requirements for boxed warnings of potential adverse effects, have had a lasting effect on clinician- and patient-related concerns regarding the use of hormone therapy (Barlow, 2014; Thompson et al., 2017). (See Chapter 8 for additional discussion.)

In recent years, certain health care providers and patients have turned to custom- compounded drugs as an alternative treatment for hormone-related health concerns. These treatments, often marketed as "bioidentical"

or "natural," are commonly referred to as compounded bioidentical hormone therapy (cBHT) (Gass et al., 2015).[1,2] Evidence suggests that millions of men and women may use cBHT and that there may be thousands of potential compounded hormone formulations that patients can purchase with a prescription. Media influences and targeted marketing approaches and claims have led many patients and certain prescribers to perceive cBHT preparations as safer and more effective alternatives to FDA-approved hormone products (Fishman et al., 2015; Thompson et al., 2017). However, compounded preparations are exempt from certain federal requirements for pharmaceuticals and are not required to demonstrate safety and efficacy.[3] In addition, some patients have a mistaken belief that *bioidentical* hormone therapy (BHT) medications are only available through custom preparation at compounding pharmacies (Files et al., 2016), even though FDA has approved several bioidentical hormone products at different doses and with various routes of administration (FDA, 2019).

In light of the fast-growing popularity of cBHT preparations, the safety, effectiveness, and use of these medications has become a substantial public health concern for various stakeholders, including medical practitioners, patients, health advocacy organizations, and federal and state public health agencies.

STUDY CHARGE

To explore the complex issues surrounding cBHT, FDA in fall 2018 requested the National Academies of Sciences, Engineering, and Medicine (the National Academies) appoint an ad hoc committee to assess the clinical utility of treating patients with cBHT. The resulting Committee on the Clinical Utility of Treating Patients with Compounded Bioidentical Hormone Replacement Therapy was charged to review the uses of cBHT preparations and the available evidence that would support marketing

[1] As a consequence of cBHT marketing strategies, the term *bioidentical* is often misinterpreted by the general public. The committee intentionally includes the term when referencing certain types of hormone therapies, with the rationale that *bioidentical* serves as an important identifier for many compounded hormone therapies, and including the term may be a useful means of more effectively communicating the report conclusions to the general public. It should be noted, however, that the committee's use of the term *bioidentical* should not be interpreted as an endorsement.

[2] For the purposes of this report, the word *replacement* was removed from the term *bioidentical hormone therapy* to avert implications that the goal of hormone therapy is to replace hormone concentrations to the levels present in young adults. The official National Academies' language regarding the committee and its task still maintains the use of the original term.

[3] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

BOX 1-1
Statement of Task

An ad hoc committee of the National Academies of Sciences, Engineering, and Medicine (the National Academies) will conduct a study to assess the clinical utility of treating patients with compounded bioidentical hormone replacement therapy (BHRT) drug products. The committee will:

- Review the current and historic use of compounded BHRT drug products to treat patients, including information about the medical condition(s) these compounded drug products have been used to treat;
- Describe the physical and chemical characteristics of compounded BHRT 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 BHRT drug products; and
- Based on the available evidence, summarize findings and make recommendations with respect to:
  - The clinical utility of compounded BHRT drug products;
  - Whether the available evidence of safety and effectiveness supports use of compounded BHRT drug products to treat patients; and
  - The patient populations that might need a compounded BHRT drug product in lieu of an FDA-approved drug product.

claims of the safety and effectiveness of cBHT preparations.[4] The committee was asked to assess whether the available evidence suggests that these preparations have clinical utility and safety profiles warranting their clinical use, and it was asked to identify patient populations that might benefit from cBHT preparations in lieu of FDA-approved BHT. The committee's Statement of Task is presented in Box 1-1.

[4] While the terms *effectiveness* and *efficacy* are similar, they are not the same. The effectiveness of a drug refers to its therapeutic effect in real-world settings. The efficacy of a drug refers to the therapeutic effect in controlled clinical settings—such as phase 2 or phase 3 randomized clinical trials. This difference is critically important. Given the limited efficacy data for cBHT preparations, the committee considered clinical studies of effectiveness, in addition to clinical studies of efficacy, in its examination of clinical utility of cBHT preparations. Owing to its broader application to the body of research reviewed, the term *effectiveness* is used more generally across the report.

STUDY SCOPE

The committee systematically reviewed the available evidence relevant to each component of the clinical utility definition, within the limits of the committee's resources, study timeline, and study scope. The committee maintained a prioritized focus on cBHT preparations of interest to the study sponsor (NASEM, 2019). These included cBHT preparations containing estradiol, estrone, estradiol cypionate, estriol, dehydroepiandrosterone (DHEA), pregnenolone, progesterone, testosterone, testosterone cypionate, and/or testosterone propionate, many of which serve as the hormonal ingredients within the most commonly prescribed cBHT formulations (see Chapters 5 and 6). Other hormone therapies commonly available through compounding, such as thyroid medications or human growth hormone, are not covered in this report.

The report looked solely at compounded drugs prepared within the regulatory framework outlined in the compounding provisions of the Federal Food, Drug, and Cosmetic Act;[3] hormones sold as dietary supplements (e.g., vitamin D) were not considered relevant to this report. Additionally, the report focuses on the use of cBHT resulting from traditional prescriber–pharmacist–patient triads, although there is limited discussion of online purchases and office stock where pertinent.

Based on the physiological effects and indications of the steroid hormones the committee reviewed, the primary focus of this report is on the use of cBHT preparations to treat menopause or male hypogonadism symptoms. The committee acknowledges that men of various ages use compounded bioidentical testosterone formulations for improvement in physical appearance and/or athletic or physical performance enhancement, resulting in the potential for nonclinical abuse. The committee reviewed evidence supporting the use of cBHT in men in this report, but given the reported magnitude of use of cBHT in women (McPherson et al., 2019), the report places a greater focus on this patient population.

KEY DEFINITIONS

Clinical utility is a multidimensional, context-dependent term for which no standardized definition exists. However, based on review of the literature, including peer-reviewed articles, consumer surveys, and formal position statements and guidelines, the committee developed, for the purposes of this report, its own definition of the term. Here, clinical utility is defined as a multidimensional construct that reflects evidence about safety, effectiveness, and therapeutic need.[5] Patient preference is also a component of

[5] In the context of this report, *therapeutic need* relates to the treatment of menopausal and male hypogonadism symptoms.

BOX 1-2
Identified Themes in the Literature on Clinical Utility

Based on insights from the literature, an entity said to have *clinical utility* has been described as being able to:

- Optimize treatment and short- and long-term health outcomes
- Affect diagnostic testing processes
- Assist with patients' decision making
- Offer psychological benefits to the patient, including improved health literacy
- Improve society

Furthermore, the evidence describing the components of clinical utility is not confined to randomized controlled trials; rather, it takes into account a broad range of factors, including:

1. The current standard of care
2. The care setting
3. Costs of care and tests
4. The nature of what is being evaluated for clinical utility

SOURCES: Ahn et al., 2019; Bagheri et al., 2019; Canter et al., 2019; Challener et al., 2019; First et al., 2019; Grosse and Khoury, 2006; Ishikawa et al., 2019; Johansen Taber et al., 2019; Lee et al., 2019; Lesko et al., 2010; McCormack and Billings, 2015; Michel et al., 2019; Miller et al., 2019; NASEM, 2018; Oh et al., 2019; Osumi et al., 2019; Setlur Nagesh et al., 2019; Soh and Aw, 2019; Teutsch et al., 2009; Vlahos, 2019; Zago et al., 2018.

clinical utility, reflecting patients' individual decision making based on how each person accepts benefits and risks. Evidence-based decisions regarding the clinical utility of a test, treatment, or medical intervention may evolve over time with additional studies (NASEM, 2016). See Box 1-2 for an overview of main themes of clinical utility and Box 1-3 for key definitions of terms used in this report.

STUDY APPROACH

To address the study charge, the National Academies appointed a 12-member committee of experts to address objectives in the Statement of Task (see Appendix D for biographical sketches of the committee members and staff). The committee met in person five times and held four half-day virtual meetings. In addition to its closed-session meetings, the committee held five public information-gathering sessions and evaluated the

BOX 1-3
Key Definitions

Bioidentical: Sometimes referred to as *bio-identical* or *bio identical*, this term describes hormones that are chemically and structurally identical to those produced by the human body, with the implication that an identical structure translates to an identical physiologic response as endogenous hormones. Bioidentical hormones may be synthesized from plant or animal sources or completely synthesized chemically, and they are offered both as products approved by the U.S. Food and Drug Administration (FDA) and as preparations that have not undergone FDA approval.

Clinical utility: A multidimensional construct that reflects evidence about safety, effectiveness, and therapeutic need. Patient preference is also a component of clinical utility, reflecting patients' variable acceptance of benefits and risks.

Compounded preparation: A nonsterile or sterile drug or nutrient preparation formulated in a licensed pharmacy, outsourcing facility, or other health care facility in response to or in anticipation of a prescription or a medication order from a licensed prescriber. Federal law permits compounding; however, these drugs are not FDA approved for safety and effectiveness.

Compounding: Drug compounding is often regarded as the process of combining, mixing, or altering ingredients to create a medication tailored to the needs of an individual patient.

FDA-approved drug product: A finished dosage form containing a drug substance, generally, but not necessarily in association with other active or inactive ingredients, that has demonstrated safety and effectiveness and received FDA approval. FDA-approved drug products will appear in FDA's *Orange Book* (FDA, 2020a).

Hormone therapy: A therapeutic treatment that alters the levels of hormones in the body in order to alleviate symptoms and clinical findings.

NOTES: See Appendix C for additional key terms. The term *bioidentical* is often confused with the term *biosimilar*. For a description of the term *biosimilar*, see FDA, 2020b.

peer-reviewed literature and gray literature (e.g., research reports, books for a lay audience) on topic areas relevant to the study's charge.

In recognition of the limited information available addressing the use, safety, effectiveness, and patient perspectives of cBHT, the committee also made concerted efforts to collect and review relevant anecdotal, survey, and

(when possible) quantitative data from national stakeholders to supplement its research efforts. For example, relevant data were submitted by the following:

- FDA
- Professional Compounding Centers of America
- National Association of Boards of Pharmacy
- Select state boards of pharmacy
- A state attorney general's office
- Representatives of 503A compounding pharmacies and 503B outsourcing facilities
- An editor-in-chief of a leading compounding journal
- Nonprofit medical and pharmaceutical societies and organizations
- Compounding advocacy organizations
- Nonprofit wellness organizations
- Women's health advocacy groups
- Medical prescribers and researchers of cBHT

In addition, the committee reviewed submitted testimonies from thousands of patients who use cBHT.

The committee used the compiled, multitiered evidence base to formulate findings, conclusions, and actionable recommendations to inform FDA on the clinical utility of cBHT and its use in the treatment of patients. Box 1-4 provides details of the committee's supplemental information-gathering process. (See Appendix A for additional details of the study approach.)

REPORT ORGANIZATION

The remainder of this report provides a more thorough discussion of cBHT in response to the Statement of Task. Chapter 2 provides an overview of the history of compounding, reviews its complexity as an art and a science, and provides a summary of the current compounding market. Chapter 3 provides an overview of the regulatory framework for compounded mediations and includes a discussion on the development, evaluation, and approval of FDA-approved products to highlight differences in regulatory processes to ensure safety and effectiveness. Chapter 4, serving as important context for the remainder of the report, provides an overview of the synthesis, structure, and biochemistry of steroid hormones, and clarifies the term *bioidentical* hormone.

Chapter 5 provides an extensive review of the available cBHT preparations and, where relevant, discusses FDA-approved BHT products to provide relevant comparisons of formulation procedures and quality testing.

BOX 1-4
Information-Gathering Process

The committee used various sources to supplement its research and review efforts. The committee met in person five times and held one half-day virtual meeting. In addition to its closed-session meetings, the committee held five public information-gathering sessions. Participants in these supplemental information-gathering processes included a range of subject matter experts, policy experts, officials representing various stakeholder organizations (e.g., compounders, women's health advocates, medical societies), and members of the general public. See Appendix A for additional details.

Public Information-Gathering Sessions—Discussion Panels

- Discussion of the Committee's Charge
- Background on Compounding
- Marketing and Use
- Context for the Current Study
- Consumer Engagement, Education, and Medical Care
- Pharmaceutical Sciences and Compounding
- Common Formulations
- Difficult to Compound List
- National Perspectives on the Behalf of Compounding Professionals
- Provider Education and Medical Care
- Pharmaceutical Sciences and Compounding Pharmacies
- 503B Outsourcing Facilities

Chapter 6 examines the available evidence on the bioavailability of the hormones included in cBHT preparations. Chapter 7 outlines the key findings and conclusions that resulted from the committee's literature review on the safety and effectiveness of hormone ingredients commonly used in cBHT preparations. This chapter also addresses the importance of adverse event reporting, a critical component in assessing the safety of publicly available medications. Chapter 8 reviews the evidence related to the current use of cBHT by patients, including the overview of the current clinical guidance for use, patterns and trends of use, and psychosocial factors that affect patient preference. The final chapter, Chapter 9, summarizes the major report conclusions supported by the evidence presented in Chapters 2 through 8 and delves into the committee's overall conclusion regarding the clinical utility of cBHT for treating patients. This final chapter also presents the committee's six recommendations to the stakeholders of the report.

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2

An Overview of Compounding

Compounding is the process of combining, mixing, or altering ingredients to create a medication tailored to the needs of a patient (FDA, 2017).[1] Compounding is most often practiced by a licensed pharmacist, a licensed physician, or a person under the supervision of a licensed pharmacist (FDA, 2017).[2] The traditional compounding process begins with a prescription created by the prescriber responding to a patient need. The prescriber customarily chooses the active ingredient(s), dosage form, dose, dosing intervals, and route of administration when writing the prescription. The prescriber may also choose inactive ingredients, especially in cases where a patient has a documented allergy to an inactive ingredient, such as peanut oil. This is followed by the compounding pharmacist preparing (e.g., formulating) and dispensing the medication to the patient.

Compounded medications may offer therapeutic alternatives for patients with unique medical needs that cannot be met by U.S. Food and Drug Administration (FDA)-approved drugs (FDA, 2018; Gudeman et al., 2013; USP, 2017). For example, compounding can provide customized formulations to (1) create alternate dosage strengths or forms, and (2) omit components of FDA-approved drugs to which a patient has an allergy.

[1] In an effort to provide additional guidance, the United States Pharmacopeia (USP) offers a more detailed definition of compounding: "the preparation, mixing, assembling, altering, packaging, and labeling of a drug, drug-delivery device, or device in accordance with a licensed practitioner's prescription, medication order, or initiative based on the practitioner–patient–pharmacist–compounder relationship in the course of professional practice" (USP, 2017).

[2] At times throughout the report, the term *compounder* and *pharmacist* is used interchangeably to describe certain professional practices related to compounding.

Compounding can also fill gaps in cases of shortages and discontinuations of FDA-approved drugs (Glassgold, 2013; USP, 2017).

Patient populations that have traditionally benefited from customized compounded formulations include pediatric patients, people at the end of life who may have difficulty swallowing pills or capsules, or people with certain specific medical conditions for which a current FDA-approved medication does not exist (Kochanowska-Karamyan, 2016; USP, 2017). Compounding differs from pharmaceutical industry drug manufacturing in that the volume of drugs prepared and prescriptions dispensed is small in relation to FDA-approved medications. See the chapter section "Compounding Market: Supply and Demand" below for insights on the recent growth of the compounding market.

COMPOUNDING: TYPES AND SETTINGS

Currently, the regulation of compounding—including rules related to the allowance and prohibition of compounding—is addressed at the federal level under the Federal Food, Drug, and Cosmetic Act (FDCA).[3] Compounding can use FDA-approved drugs as a starting point, and alter them in some way, such as combining or diluting them. Compounding can also start with bulk substances (active pharmaceutical ingredients [APIs]) and combine them with excipients (inactive ingredients) to produce the final compounded preparation. In addition, compounded drugs are prepared either as *sterile* or *nonsterile* preparations. In sterile compounding, drug formulations are prepared in a clean-room environment using aseptic techniques to ensure preparations are free of microorganisms. Sterile compounding is used primarily for injectable, implant, and ophthalmic preparations. In nonsterile compounding, drug formulations are prepared in a clean environment but without aseptic techniques required. Nonsterile compounding is used primarily to prepare oral and topical (skin) formulations: capsules, solutions, suspensions, ointments, creams, and suppositories. Both sterile and nonsterile drug formulations are produced within a wide range of pharmaceutical and medical settings.

Compounding can occur in community pharmacies, physicians' offices, and hospital pharmacies; these are referred to in this report as *503A compounding pharmacies*. Compounding, particularly in smaller, independent community pharmacies, remains an important component of pharmacy practice (McPherson et al., 2006). In fact, studies suggest that the preparation of compounded formulations at community pharmacies may strengthen the patient–pharmacist relationship, improve pharmacists'

[3] See Chapter 3 for an overview of the federal and state-level regulations and oversight for compounding preparations.

professional satisfaction and perceived quality of patient care, and imbue pharmacists with a greater responsibility to provide patient-centered care (McPherson and Fontane, 2010; Yancey et al., 2008).

Public testimony to the committee provided additional insights into the expanding compounding market. Based on submitted testimony, certain 503A compounding pharmacies no longer function primarily as community pharmacies but rather as large corporations that dispense compounded preparations to thousands of patients across state lines.[4]

In 2013, Congress created a new category for compounding drugs in larger amounts at specialized compounding facilities, referred to in this report as *503B outsourcing facilities*. Given that certain requirements are met, these compounding facilities can produce and ship large volumes of drugs across state lines and produce compounded preparations for third parties, such as hospitals, clinics, and physician offices without a prescription (Glassgold, 2013).[5]

In either compounding setting (503A compounding pharmacy or 503B outsourcing facility), the United States Pharmacopeia (USP) provides environmental guidelines, suggesting that compounded drugs should be developed in designated areas that are adequately designed to support the sterile or nonsterile processes, including providing proper storage for those preparations and the appropriate conditions (e.g., designated temperature, light, moisture, ventilation, and security) (USP, 2017). Box 2-1 provides details about the regulations for allowable compounding under the FDCA.

THE COMPLEXITY OF COMPOUNDING

There is a unique art and science behind compounding drugs. It is the compounder's responsibility to prepare the compounded drug preparation with the proper dose of the API and the appropriate quality and purity of all ingredients while maintaining sanitary, and if necessary, aseptic conditions when preparing a compounded drug preparation. The compounder must also provide the patients and their families with the proper instructions through clear labeling or face-to-face consultation (USP, 2014). See Box 2-2 for an overview of the importance of a Master Formulation Record as a component of quality control during the formulation of a drug.

For the development of more complex compounded formulations, a professional specializing in formulation science may be needed. Formulation science is critical in the development, manufacturing, and testing of chemical (including pharmaceutical) products and preparations. Such

[4] Open session testimony, November 2019.

[5] Under federal law, 503B outsourcing facilities may also compound for patient-specific prescriptions. See the Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

BOX 2-1
Allowable Compounding Under the Federal Food, Drug, and Cosmetic Act

Compounding After Receipt of a Valid Prescription

A prescriber may write a prescription for an identified individual patient who needs a compounded preparation.[a] As a common next step, either the prescriber or the patient then brings or sends the prescription to the 503A compounding pharmacy, where the pharmacist creates the compounded drug preparation for the patient according to the prescription. In other cases, a prescriber may place an order in a patient's health record for a compounded drug preparation, which in most cases is provided by the health care facility's pharmacy.

Compounding Before Receipt of a Valid Prescription Order

In certain situations, a pharmacist or physician may compound a batch of drugs in anticipation of receiving a patient-specific prescription. This is allowed in cases where there is a history of receiving prescriptions for a particular drug to be compounded for an identified individual patient and/or in the context of an established relationship with a particular prescriber or patient (The Pew Charitable Trusts and NABP, 2018). Having limited quantities of anticipated compounded preparations on hand may reduce the time it would take for a compounded drug preparation to be made available to a patient upon receipt of a valid prescription order for that patient.

Compounding for Office Stock

Hospitals, clinics, and health care practitioners can obtain non-patient-specific compounded drug preparations from outsourcing facilities registered under Section 503B (The Pew Charitable Trusts and NABP, 2018). This "office stock" can increase efficiency and reduce the likelihood of human error that is associated with compounding batches of a drug preparation after the receipt of individual prescriptions for the same drug. On the other hand, formulating large batches of drugs is associated with additional risks, including contamination and creating subpotent/superpotent drug preparations, which would affect a much larger group of patients (The Pew Charitable Trusts, 2016).

[a] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

BOX 2-2
Master Formulation Record According to USP <795> for Compounded Nonsterile Products

A Master Formulation Record (MFR) is a reference (derived from an individual patient prescription, or a medication order) that fully describes the formula for the preparation to be dispensed (USP, 2014). If an MFR does not already exist in the pharmacy, the compounder must create it.[a] In doing so, the compounder will likely draw from one or more of the following information sources: databases (e.g., online chemical databases; commercial compounding formula databases; not-for-profit organization databases), established compounding text books and journals, or colleagues.[b] An MFR must include the following information (USP, 2014):

- Name, strength or activity, and dosage form
- If applicable, calculations involving quantities, concentrations, strength
- Identities, amounts, characteristics of all components
- Complete preparation instructions, including description of necessary equipment when appropriate
- Container, closure system(s), and packaging and storage requirements
- Physical description of the final product
- Reference source to support the assigned beyond-use date and storage requirements
- Legally required labeling requirements in addition to the name, quantity, or concentration of each API; assigned beyond-use date and storage requirements; prescription or control number; quality control procedures; and expected results

Once the MFR is completed, an associated Compounding Record is developed that will document each batch of product prepared (USP, 2008, 2014). While generally considered best practice, these processes are not required in states that choose not to adopt USP <795> or equivalent standards.[c] MFRs are an important component of quality control during the formulation of a drug. If a Compounding Record deviates from what is written in an MFR without proper documentation for such a change, it is a breach in the quality control that aims to provide patients with consistent formulations of their prescription.

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[a] As of April 2020, MFRs are only required for certain compounding (nonsterile compounding in 503A compounding pharmacies in states that have adopted USP <795>), though similar documentation is also required in current good manufacturing practice regulations. See written procedures; deviations. 21 CFR 211.100 (April 1, 2019).

[b] Example databases include National Library of Medicine (NLM, 2020); Professional Compounding Centers of America (PCCA, 2019); MEDISCA (Medisca, 2019);

continued

BOX 2-2 Continued

LETCO (Letco Medical, 2019); Spectrum (Spectrum Pharmacy Products, 2019); CompoundingToday (IJPC, 2019).

[c] The United States Pharmacopeial Convention (USP) is a nonprofit organization that works to ensure the quality of compounded medicines by setting public standards for identity, strength, quality, and purity. USP developed three types of standards for compounding: USP-National Formulary monographs for bulk drug substances, USP compounded preparation monographs, and essential General Chapters. USP does not have regulatory or enforcement authority, but certain USP standards are enforceable in some states under state law. In 2019, USP released new versions of standards, but to date, those versions are not yet official and may be changed.

formulation experts apply established science and are able to guide decisions about quantities and combinations of active and inactive ingredients, incorporate quality procedures, and test for stability. This level of expertise is especially essential for the development of complex medications (e.g., sustained released medications, pellets). Of critical importance, a compounding pharmacist often does not have the same training or experience as a formulation scientist, nor access to the same data for evaluation and determination of quality, stability, and effectiveness.

Seemingly small variations in compounding processes, such as the order in which ingredients are added, the temperature at which the formulation is prepared, or the time allotted to mixing ingredients, can lead to significant differences in the performance of the resulting drug preparation (Chang et al., 2013). Unlike manufacturing protocols for drugs that FDA approves to reliably ensure that a safe and effective product results every time, compounding procedures are not standardized nor tested for their ability to produce safe and effective drug preparations. For example, delivery of active ingredient doses above the desired therapeutic level could result from miscalculation, including too much API in the formulation, or from poor quality formulation resulting in an erratic and unpredictable release rate; the latter has been observed with compounded pellet formulations (Jiang, 2019).

Polypharmacy, when a single patient is simultaneously taking multiple medications to treat one or more medical condition, as well as potential drug–drug interactions add to the considerations pertinent to the compounding process. While concerns for drug–drug interactions are not unique to compounding, the combination of multiple drugs into a single dosage form without prior testing for safety and effectiveness is of concern, particularly for formulations that include multiple drugs within a similar

therapeutic class. For example, compounders should account for the fact that testosterone can be directly metabolized to estradiol, and that patients receiving a combination of testosterone and estradiol may inadvertently receive a higher dose of estradiol than intended (Ishikawa et al., 2006).

Training and Oversight for Compounders

While standard pharmacy school curricula generally include some basic training in compounding, additional training and certification are needed to become skilled at compounding, particularly for formulations that are complex or contain multiple active ingredients. Compounding pharmacists would also benefit from education that extends beyond the basic skills, but relatively few have specialized training or higher certification (Schommer et al., 2008). Organizations such as the Professional Compounding Centers of America and the American College of Apothecaries offer classes, both live and online, and certification programs. Starting in the fall of 2019, the Board of Pharmacy Specialties began offering an exam for pharmacists to become accredited in Compounded Sterile Preparations, though the specialty has yet to receive official recognition (Board of Pharmacy Specialties, 2020).

Many states expect compounders to adhere to standards of practice established by USP (The Pew Charitable Trusts and NABP, 2018):

> to minimize harm, including death, to human … patients that could result from (1) excessive microbial contamination, (2) variability from the intended strength of correct ingredients …, (3) physical and chemical incompatibilities, (4) chemical and physical contaminants, and/or (5) use of ingredients of inappropriate quality. (USP, 2014)

However, because USP has no power to enforce practice compliance, it is up to the state legislature or state pharmacy boards to adopt, oversee, and enforce the quality standards for compounding set by USP. Such oversight varies significantly from state to state.

Statements from pharmacy associations, including the American College of Clinical Pharmacy, American Society of Health-System Pharmacists, and National Association of Boards of Pharmacy, echo the considerations outlined earlier in this chapter. While all of these organizations recognize the importance of drug compounding, they also express concern regarding the lack of standardized, well-studied formulas; the scarce education and information on compounding provided to patients, prescribers, compounders, and regulators; the lack of evidence on the safety or effectiveness of compounded bioidentical hormone therapy (cBHT); and the increasing exposure of patients to compounded preparations that pose greater risk

than FDA-approved products. (See Chapters 6 and 7 for a discussion on the available evidence on the bioavailability, safety, and effectiveness of compounded hormone preparations.)

THE COMPOUNDING MARKET: SUPPLY AND DEMAND

Compounding was the primary route by which medications were produced until early in the twentieth century, when the advent of large-scale pharmaceutical manufacturing led to a decreased reliance on compounding (Newton, 2003; Sundberg, 1997). However, over the last few decades, the increasing demand for personalized medical care—coupled with the lack of regulations and oversight for the development of compounded medications—has catalyzed a resurgence in compounding and engaged a much broader patient population than traditionally intended (Gameiro et al., 2018; Gudeman et al., 2013; Oroszlan, 2016).[6]

The growing demand for compounded drugs is also reflected in their use to treat a wide spectrum of conditions across a range of therapeutic areas, including men's and women's health, pain management, sports medicine, dental care, veterinary care, pediatrics, hospice care, and in their use in the fields of allergy, dermatology, immunology, otolaryngology, oncology, ophthalmology, neurology, and rheumatology (Glassgold, 2013; McPherson et al., 2016; NABP, 2017).[7] Public health officials have become concerned about this expansion of the compounding market because it increases the number of patients with the potential to be exposed to drugs that have not undergone the same rigorous production processes and quality controls as FDA-approved drugs (FDA, 2017).[8]

Compounding Services and Data on General Use

Given its rise in popularity over the past 2 decades, compounding has become an increasingly lucrative industry. Unfortunately, it is difficult to identify publicly available, evidence-based estimates of the number of drugs compounded, the types of drugs compounded, the number of pharmacists and physicians who compound, or the size of the compounding market (Glassgold, 2013). This lack of data likely results from the lack of federal reporting requirements and centralized data collection, as well as variable insurance coverage for a broad range of compounded medications (NASEM,

[6] See Chapter 3 for an overview of the federal and state-level law, regulations, and oversight for compounding preparations.

[7] A discussion on the trends in the marketing of cBHT preparations can be found in Chapter 8.

[8] Chapter 3 provides an overview of how policies and regulations have dealt with marketing for compounded drugs.

2019). Specifically, there is no requirement for 503A compounding pharmacies to report or publicly advertise the presence and/or extent of their compounding capabilities (e.g., nonsterile or sterile; small focus versus primary specialty). Although outsourcing facilities must report their 6-month compounding totals to FDA, only some 70 facilities have registered voluntarily and identified themselves as outsourcing facilities, and it is likely that other nonregistered facilities exist and are operating in violation of Section 503A without appropriate oversight for the compounding they perform.[9] The resulting data shortage poses challenges for risk–benefit assessment and public health policy related to compounded drug preparations.

With this context in mind, the National Council for Prescription Drug Programs estimates that there are more than 32,000 pharmacies nationwide that broadly describe some compounding activities under their offered services (Pew Charitable Trusts, 2016). In terms of specialization, the American Pharmacists Association estimates that only around 7,500 of the approximately 56,000 community-based U.S. pharmacies specialize in providing compounding services, meaning the pharmacists in those facilities spend most or all of their time compounding special preparations for patients (American Pharmacists Association, 2019). The Alliance for Pharmacy Compounding reports that 1 to 3 percent of prescriptions in the United States are for compounded drugs (APC, n.d.). Additionally, a 2019 Letco Medical survey of more than 4,000 pharmacy compounders found that nearly 40 percent of those surveyed worked in pharmacies solely dedicated to compounding (APC, n.d.).

Other data provide additional insights into the scope of the compounding world. From 2005–2016, the number of Medicare patients receiving a compounded drug increased 281 percent (HHS OIG, 2016). Similarly, a study of individuals with private insurance found an increase of 27 percent in compounded drug use between 2012 and 2013 (McPherson et al., 2016). A 2019 survey of 494 patients found that almost 80 percent of people who received compounded prescriptions did so through mail-order pharmacies, and that among those surveyed, compounded prescriptions were being used to replace rather than supplement other drug(s) (McPherson et al., 2019).

Data on compounded drugs are also available from national workers' compensation claims. Compounding is a growing trend in workers' compensation programs; prescriptions for compounded drugs increased almost five-fold between 2007 and 2012, from 6,416 to 30,669 (Walls et al., 2014). Several surveys of pharmacists and prescribers have sought to elicit information about the use of compounded drugs, but the information obtained has been limited because of low response rates (McPherson et al., 2019; Ness et al., 2002; Warner and Tuder, 2014).

[9] These points are discussed in greater detail in Chapter 3 of this report.

Insurance claims data also show that the number of beneficiaries receiving compounded drugs increased by 281 percent, from 73,368 in 2006 to 279,873 in 2015 (HHS OIG, 2016). A retrospective analysis of prescription claims data found that the prevalence of eligible members using compounded drugs increased by some 27 percent between 2012 and 2013, with 1.4 percent of eligible members using compounded drugs in 2013. The number of claims for compounded drugs also increased by some 34 percent (from 486,886 to 653,360) during the same period (McPherson et al., 2016).

Market Reports

Several private marketing reports have estimated the global market revenue for compounded preparations to fall between $2 and $9 billion. Those analyses all predict growth in the next few years, ranging from 3 to 7 percent. A caveat is that these estimates come from private marketing reports and are based on data sources that are publicly unverifiable (e.g., Bourne Partners, 2018; Global Market Insights, 2018; Market Research Engine, 2018; Ugalmugale and Mupid, 2018a,b; Zion Market Research, 2018). Other unverifiable analyses have estimated the global market for compounding pharmacies in 2017 to be $8.5 to $9 billion, with the 503B market estimated at $1.5 billion (Bourne Partners, 2018; Global Market Insights, 2018; Zion Market Research, 2018). These analyses project that by 2022 to 2024, the global compounding market will reach $10 to $14 billion, with a compounded annual growth rate of 4 to 6 percent (Bourne Partners, 2018; Global Market Insights, 2018; Market Research Engine, 2018; ReportsnReports, 2018; Zion Market Research, 2018).

Given the evidence for the substantial use of compounded drugs and the minimal federal and state oversight and protection for patients, there is cause for serious concern that an increasing number of drugs used in the United States are consumed without assurance for their quality, safety, and effectiveness. Chapter 3 reviews the current federal and state-level regulatory framework to minimize risks related to the use of compounded preparations, and Chapter 7 discusses the scientific evidence on the safety and effectiveness of compounded bioidentical hormone preparations, and related adverse events.

Conclusion 2-1

Compounding is a necessary component of medical and pharmaceutical practice and offers therapeutic options to patients with medical needs that cannot be met by available FDA-approved drug products. However, the lack of publicly available data about the number of pharmacies providing compounding services, and the overall supply of and demand for the different formulations precludes the ability to understand the scopes of the compounding industry and potential public health concerns, and as a result, hinders efforts to characterize the safety and effectiveness of compounded bioidentical hormone therapy preparations.

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3

Regulatory Framework for Compounded Preparations

Compounded drugs have long been part of the medical armamentarium. Through drug compounding, compounders may offer therapeutic alternatives for patients with unique medical needs that cannot be met by U.S. Food and Drug Administration (FDA)-approved drug products (FDA, 2017a). The Federal Food, Drug, and Cosmetic Act (FDCA) of 1938 is the primary source of FDA's authority over prescription drugs. To help protect the public from ineffective or potentially dangerous products, prescription drug manufacturers have been required to submit evidence of the safety of drugs since 1938, and of their efficacy since 1962, before they can be sold in the United States (Kim, 2017).[1] Although compounded drugs require a prescription prior to being dispensed to patients, the FDCA does not give FDA similar authority to evaluate their safety, effectiveness, or quality before they are marketed (FDA, 2017a). In the absence of substantial federal oversight, states remain the primary regulators for the majority of prescription-based drug compounding practices (Kim, 2017).

This two-tiered system of regulatory oversight of the U.S. drug market—in which FDA primarily oversees the production of manufactured drugs and states primarily oversee compounded drugs (Kim, 2017) —is the subject of this chapter. It begins with a comparison of the federal regulatory structures for manufacturer-distributed drugs versus

[1] P.L. 87-781, 76 Stat. 780 (1962) (current version as amended at 21 U.S.C. §§ 301–392).

compounded drugs, and then it reviews key regulatory issues related to the U.S. compounded drug market.[2]

FDA-APPROVED DRUG PRODUCTS

FDA approves a new drug for public use only after careful review of data from preclinical studies in animals and human clinical trials that determine whether the benefits of the drug outweigh its known and potential risks. FDA's direct involvement begins after the drug sponsor has gathered sufficient preclinical information to warrant testing in humans; this information includes the drug's chemical and physical properties; biochemical properties, such as solubility; metabolism; and factors influencing the pharmacokinetics and pharmacodynamics of the drug (FDA, 2016a, 2020b).

At that point, and before beginning clinical testing, the drug sponsor must submit the results of its preclinical testing to FDA in an investigational new drug (IND) application. The IND application, in addition to plans for human clinical trials, also includes information about the proposed manufacturing process to ensure that the company can produce consistent batches of the drug. Human trials can start 30 days after submission of the IND, allowing FDA time to review the information to ensure that participants will not be exposed to undue risk (FDA, 2020b).[3]

Drugs covered by an IND generally undergo a multistage process of human clinical testing. The first phase of clinical trials is designed to assess how the drug is metabolized and excreted; to identify the most frequent, acute safety issues; and to evaluate different dosing levels, usually in a small number of healthy volunteers.[4] Phase 2 trials gather initial data about drug activity (often as measured by surrogate endpoints, such as changes in biomarkers) and adverse effects in a larger number of individuals who have the condition or disease the product is intended to treat. These trials may continue to evaluate a range of doses to determine the optimal dose with respect to both efficacy and safety.

Phase 3 trials are typically randomized controlled trials that compare the safety and efficacy of the drug with a placebo or another product approved for the proposed indication. These trials may also study different populations and different dosages of the drug; in some cases, the drug may

[2] Several of the hormones covered in this report can be purchased online and in health stores as dietary supplements, including in doses and combinations similar to those available through compounded formulations. However, dietary supplements fall under a different regulatory structure than compounded drugs, and thus will not be discussed in detail in this chapter.

[3] FDA can issue a clinical hold within these 30 days if it feels the data do not yet support safe study of the drug in humans, or if clarifications are needed to provide the needed assurance.

[4] Toxic, high-risk drugs are studied only in populations with the disease or condition to be treated rather than healthy volunteers.

be studied in combination with other approved drugs to see if the combination improves outcomes. Phase 3 studies vary in size, depending on the size of the target population and the size of the effect of interest; some phase 3 studies are small, while others recruit thousands of research participants. Phase 3 trials are intended to provide the primary clinical evidence of the safety and effectiveness of the drug (FDA, 2016a). Throughout all phases of testing, study protocols are reviewed by FDA and must receive institutional review board approval (FDA, 2020b).

Depending on the results of the clinical trials, the sponsor (nearly always a pharmaceutical company) may file a new drug application (NDA) proposing that FDA approve a new product for marketing in the United States.[5] The NDA includes information about the results of relevant animal studies, results of all clinical studies, and information about the manufacturing, processing, packaging, and investigators conducting the research, as well as proposed labeling language that describes appropriate usage and potential adverse events. FDA reviews the information to determine the following:

- Whether the studies demonstrate that the drug is safe for its intended use and supported by substantial evidence of effectiveness, and whether the benefits of the drug outweigh the risks;
- The appropriateness of the manufacturer's proposed labeling, including package insert; and
- The adequacy of the manufacturing process and the controls used to maintain the drug's quality (FDA, 2019e).

After FDA approves a drug, further safety monitoring (phase 4 of the process) is critical because the clinical trials that support approval cannot predict all of a drug's effects until it is used more broadly. Manufacturers of approved drugs are required to submit regular safety updates to FDA, including results of further studies and adverse event reports they receive

[5] In addition to NDAs, there are other types of therapeutic drug applications. These include a Biologics License Application (used to approve biologics), an Abbreviated Biologics License Application (used to approve biosimilar versions of biologic drugs), and an Abbreviated New Drug Application (ANDA) (used to approve generic drugs). Approval of an ANDA requires demonstrating that the generic drug is pharmaceutically equivalent (including having the same dose of active ingredient and method of administration) and bioequivalent (including having the same pharmacodynamic properties, such as maximum serum concentration and time to achieve maximum concentration) to the original version. By meeting these requirements, generic manufacturers do not have to repeat the same battery of clinical trials for their products that led to the approval of the brand-name products serving as the reference products. For additional information, see https://www.fda.gov/drugs/how-drugs-are-developed-and-approved/types-applications (accessed May 23, 2020).

from physicians and patients.[6] FDA also collects reports of adverse events submitted directly by health professionals and patients and maintains the Sentinel System. The Sentinel System, which launched in February 2016, allows FDA to query large electronic databases of health outcomes derived largely from administrative and claims data from health insurers to identify safety signals or follow up on ones that emerge through postmarket safety reports (FDA, 2019b).

FEDERAL REGULATION OF DRUG COMPOUNDING

Throughout its history, compounding has been considered part of the practice of pharmacy. Since states are the primary regulators of various health care professions, including pharmacy and medicine, compounding is largely regulated at the state level (Glassgold, 2013). Policy makers and federal regulators generally avoided seeking to exercise authority over compounding pharmacy practice given its small scale and the individualized nature of the treatment (Kim, 2017). By the late 1980s, however, compounding had grown into a major industry. As part of an emerging wellness movement, some pharmacists advertised compounded preparations as all-natural and lower risk alternatives to FDA-approved drug products (Boodoo, 2010). In addition, certain large-scale compounding facilities began producing copies of FDA-approved drugs and marketing those products widely across state lines (Glassgold, 2013). These facilities seemed indistinguishable from traditional pharmaceutical manufacturers, except that they did not manufacture drugs in accordance with required quality standards or obtain approval from FDA (Boodoo, 2010). They would obtain state licenses as pharmacies to avoid registering with FDA as a drug manufacturer, but would deliver drugs without having patient-specific prescriptions (Snow, 2013), and in certain instances, used unapproved or withdrawn active ingredients (Kim, 2017). FDA and Congress began to address these issues through the development of guidelines and legislation.

Under the FDCA, compounded drugs are technically considered "new drugs" and thus subject to all of the law's requirements. However, since it would be impractical for pharmacists to obtain approval for each compounded drug produced to meet the specific needs of an individual patient, FDA generally did not enforce new drug approval requirements for compounded drugs.[7]

[6] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

[7] *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 369–370 (2002) ("[I]t 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.").

To clarify the agency's role in regulating drug preparations from compounding pharmacies, FDA issued a Compliance Policy Guide (CPG) in 1992.[8] The 1992 CPG listed nine actions or factors that might lead FDA to subject a compounder to FDA oversight as a manufacturer, including: production of "inordinate amounts" of drugs, using ingredients not from FDA-approved facilities, compounding existing FDA-approved products, and "soliciting business to compound specific drugs" (Kim, 2017; Snow, 2013).[9] Despite a ruling in FDA's favor from a federal court of appeals, FDA still generally did not enforce the CPG in the face of substantial criticism from the pharmacy community (Boodoo, 2010; Snow, 2013). However, in 1997 much of the CPG was incorporated into law as part of the Food and Drug Administration Modernization Act (FDAMA), and the Section 503A in the FDCA was created. This new section outlined the conditions that compounded drugs must meet to be exempt from certain aspects of the FDCA.[10] In addition, Section 503A(c) of the new law prohibited compounding pharmacies from soliciting prescriptions (Snow, 2013).[11]

In 2001, a group of pharmacies challenged Section 503A(c), arguing that using advertising as a criterion in determining whether to regulate compounding in the same manner as drug manufacturing violated compounders' commercial speech rights under the First Amendment (Kim, 2017). The Ninth Circuit agreed and invalidated all of Section 503A because of this problematic part. In 2002, the Supreme Court affirmed the Ninth Circuit's holding that Section 503A(c)'s effect on advertising was unconstitutional.[12] However, the Supreme Court did not comment on whether Section 503A's advertising restrictions were severable from the other provisions of Section 503A, so in the Ninth Circuit, all of Section 503A was considered invalid. This, in effect, eliminated FDA's ability to regulate compounding in the Ninth Circuit (Alaska, Arizona, California, Hawaii, Idaho, Montana, Nevada, Oregon, and Washington) (GAO, 2016; Kim, 2017).

FDA understood the Supreme Court's ruling to mean all of Section 503A was invalid nationwide,[13] and therefore released an updated, nonlegally binding CPG in 2002. Similar to the 1992 CPG, the new guidance document reiterated the criteria FDA would use to determine if actions were

[8] U.S. Food and Drug Administration, Compliance Policy Guide 7132.16, Manufacture, Distribution and Promotion of Adulterated, Misbranded, or Unapproved New Drugs for Human Use by State-Licensed Pharmacies, March 16, 1992.

[9] *Thompson v. W. States Med. Ctr.*, 535 U.S. (2002).

[10] Examples of the outlined conditions are described in later sections of the chapter.

[11] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

[12] See *Thompson v. W. States Med. Ctr.*, 535 U.S. (2002) and *W. States Med. Ctr. v. Shalala*, 238 F.3d 1090, 1092 (9th Cir. 2001) for additional details.

[13] Pharmacy Compounding Compliance Policy Guide; availability. 67 FR 39409 (June 7, 2002).

legitimate compounding or manufacturing subject to FDA oversight, while excluding any restrictions on promoting compounding services (GAO, 2013; Nolan, 2013; Snow, 2013).[14] In 2008, FDA regulation of compounding became more complex when the Fifth Circuit, in *Medical Center Pharmacy v. Mukasey*, concluded that Section 503A(c) was severable.[15]

In October 2012, contaminated injections from the New England Compounding Center (NECC), a large-scale drug compounding facility, led to a fungal meningitis outbreak that killed more than 60 people and injured more than 700 (FDA, 2017a). This outbreak of fungal meningitis brought national attention to the incomplete oversight of compounding. As early as 2002, FDA suspected that NECC likely used illegitimate compounding practices, and FDA had inspected NECC three times by 2004 (Kim, 2017). FDA sent a warning letter to NECC in 2006 asking the company to make its manufacturing practices safer (U.S. House of Representatives, 2013). However, FDA never required correction of NECC's problematic compounding practices (Kim, 2017). When FDA officials inspected the NECC plant in the aftermath of the outbreak, they found vials of steroids filled with enough floating contamination to be visible to the human eye (Grady et al., 2012). Partly as a result of this incident, Congress passed the Drug Quality and Security Act (DQSA) in November 2013 to clarify FDA's authority in regulating and overseeing compounded drugs.

Drug Quality and Security Act

Title I of the DQSA, called the Compounding Quality Act, amended Section 503A to remove the restrictions on soliciting prescriptions, and added the new Section 503B to the FDCA, creating a second category of drug compounding with increased federal regulatory oversight.[16] Section 503B established a new category of compounder termed *503B outsourcing facilities* that can voluntarily register with FDA to compound without a patient-specific prescription and without restrictions on interstate distribution.[17] See Figure 3-1 for a geographic distribution of 503B outsourcing facilities throughout the United States.

503A Compounding Pharmacies

Section 503A exempts drugs that meet certain conditions from three statutory FDCA requirements: new drug approval, labeling with adequate

[14] CPG § 460.200 (May 29, 2002).

[15] *Medical Center Pharmacy v. Mukasey*, 536 F.3d 383, 404 (5th Cir. 2008).

[16] Drug Quality and Security Act of 2013, P.L. 113-54, 127 Stat. 587 (codified at 21 U.S.C. § 301).

[17] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

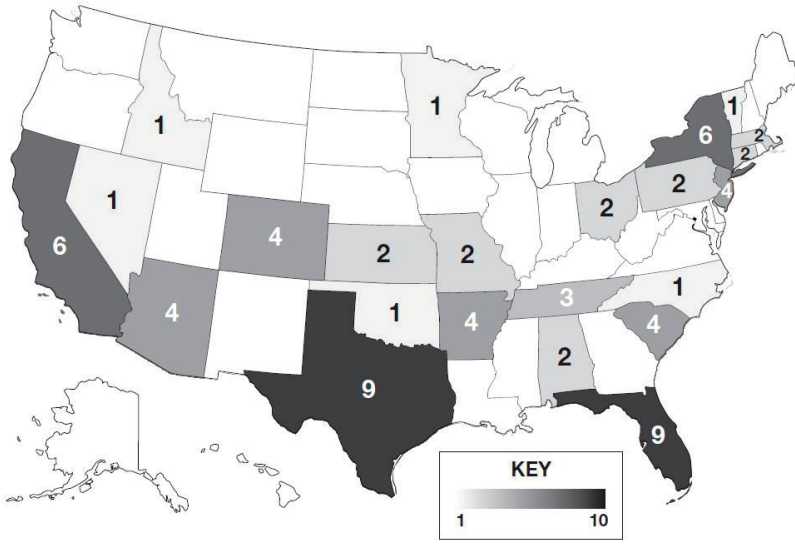

FIGURE 3-1 Geographic distribution of 503B outsourcing facilities throughout the United States.
NOTES: Darker shading reflects a greater number of outsourcing facilities in the state. Values of 503A pharmacies are difficult to estimate owing to a lack of standardized reporting, wide-ranging scopes of compounding between pharmacies, and frequent changes in the number of 503A pharmacies. See Appendix E for additional data on 503A and 503B compounding facilities.
SOURCE: FDA, 2020c.

directions for use, and current good manufacturing practice (CGMP) procedures. To be exempt from these requirements, a drug must be compounded by a licensed pharmacist or physician with a valid prescription for an identified patient, or must be compounded in limited quantities in anticipation of a prescription based on a history of prescription orders (often referred to as *anticipatory compounding*). In addition, if not compounded from an existent FDA-approved product, the drug must use *bulk drug substances* that meet United States Pharmacopeia-National Formulary (USP-NF) standards in applicable monographs, if a monograph exists.[18] Section 503A also prohibits compounding drugs that have been withdrawn as a result of safety or effectiveness concerns, present demonstrable difficulties for compounding, are essentially copies of FDA-approved drugs, or compounded within

[18] Other allowable conditions for the use of bulk drug substances in compounded preparations are discussed later in this chapter.

a state that has entered into a Memorandum of Understanding[19] with FDA, or within a licensed pharmacy (or by a licensed physician) where the compounded preparations distributed out of state do not exceed 5 percent of total prescriptions dispensed or distributed by that particular pharmacy or physician (Kim, 2017; Snow, 2013).[20]

Compounding pharmacies that qualify for Section 503A exemptions are not required to register with FDA, and FDA neither routinely inspects compounding pharmacies nor assesses the quality of the compounded preparations produced by those pharmacies (Gudeman et al., 2013). Rather, state boards of pharmacy are the primary overseers of Section 503A compounding pharmacies, leading to less consistent and comprehensive supervision than would be given by FDA and state-by-state variability in the degree of oversight (The Pew Charitable Trusts, 2016). While gaps in oversight exist, a violation of 503A, or other applicable statutes within the FDCA, may result in warning letters, product seizures, injunctions, or prosecution by state or federal authorities (FDA, 2016b).

503B Outsourcing Facilities

In addition to amending Section 503A, the DQSA added Section 503B to the FDCA, establishing outsourcing facilities, which are operations that can compound without the need for patient-specific prescriptions, though they may also compound for patient-specific prescriptions. Section 503B describes the conditions that must be satisfied for drugs compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility to qualify for exemptions from FDCA requirements for new drug approval, labeling, and drug supply chain security. Similar to 503A pharmacies, 503B facilities are restricted from compounding drugs that have been withdrawn from the market because of safety or effectiveness concerns, present demonstrable difficulties for compounding, or are essentially copies of FDA-approved drugs. Section 503B also describes separate restrictions on the use of bulk drug substances.[21] Under Section 503B, compounded drugs from outsourcing facilities are required to provide some labeling, though FDA does not review these labels for approval, and the required information for the label is minimal.[22] See sections below for an additional discussion on requirements for labels.

[19] A standard Memorandum of Understanding has not yet been finalized. A draft form of the agreement, published in 2018, can be found at https://www.fda.gov/media/91085/download (accessed April 13, 2020).

[20] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

[21] The separate restrictions for producing copies of FDA-approved drug products and using bulk drug substances are described later in this chapter.

[22] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

Outsourcing facilities are required to register annually with FDA, undergo inspections according to a risk-based schedule, and report adverse events. Outsourcing facilities must submit a biannual report to FDA identifying the compounded drugs they prepared in the past 6 months.[23] Section 503B facilities must also comply with CGMP requirements,[24] which requires additional investments in time and resources compared to those required of most 503A compounding pharmacy operations. Section 503B facilities thus have more federal oversight to ensure drug quality than do 503A compounding pharmacies.

In summary, federal oversight of the manufacturing process for FDA-approved medications and non-FDA-approved compounded medications is complex. See Figure 3-2 for a distilled graphic depiction of select steps in FDA's oversight of these processes.

Distinguishing Features of 503A and 503B Compounders

Section 503A compounders and Section 503B outsourcing facilities have other important differences. Select examples, including those related to the raw materials they can use, their ability to produce copies of FDA-approved drugs, their labeling requirements, and their ability to sell compounded preparations through interstate commerce, are discussed in the sections below. (To review additional key differences, not discussed in this section, see FDA, 2018b.)

Bulk Drug Substances

Sections 503A and 503B place limits on the bulk drug substances, or active pharmaceutical ingredients (APIs), that can be used in compounded drugs. The FDCA states that 503A pharmacies may only use bulk drug substances that (1) comply with an applicable USP or NF monograph and the USP chapter on pharmacy compounding; (2) are components of FDA-approved drug products if an applicable USP or NF monograph does not exist; or (3) appear on FDA's list of bulk drug substances that can be used in compounding.[25]

In contrast, the FDCA states that 503B facilities may only use bulk drug substances that: (1) are used to compound drug products that appear on FDA's drug shortage list at the time of compounding, distribution, and

[23] Additionally, outsourcing facility preparation reports can be found at https://www.fda.gov/drugs/human-drug-compounding/information-outsourcing-facilities (accessed April 13, 2020). These preparations are likely less diverse than those that are produced at 503A compounding pharmacies.

[24] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

[25] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

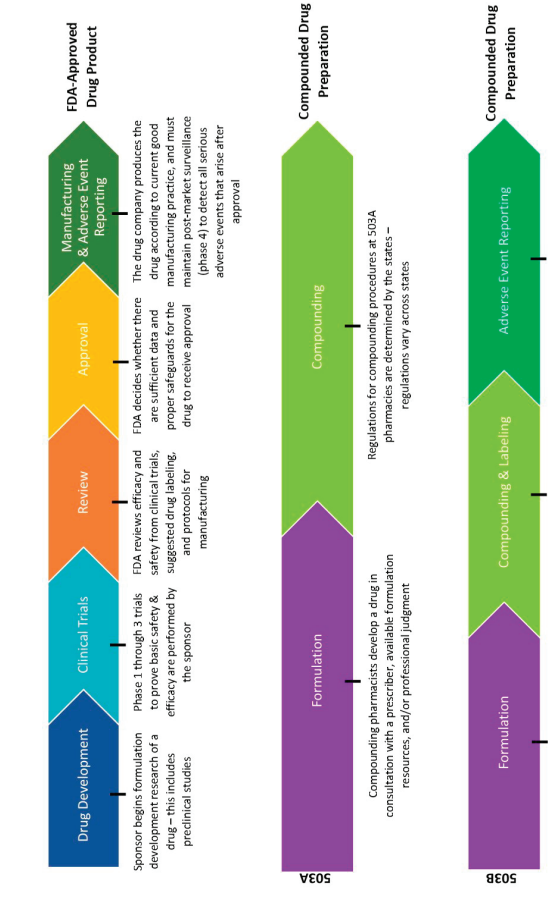

FIGURE 3-2 Comparison of select steps within the statutory and regulatory processes for FDA-approved drug products and compounded drug preparations.
NOTES: The figure is intended to provide a general overview of the statutory and regulatory processes required of FDA-approved drug products and compounded drug preparations. The figure does not offer a complete summary of the complex regulatory framework for all drug products or compounded preparations. Compounding preparations can be made from either bulk drug substances or FDA-approved products that are subsequently modified. 503B outsourcing facilities can make compounded drugs without a patient-specific prescription.
SOURCES: FDA, 2016a; Federal Food, Drug, and Cosmetic Act § 503A and § 503B.

dispensing; or (2) appear on FDA's list of bulk drug substances for which there is a clinical need.[26,27]

FDA is in the process of compiling 503A and 503B "bulk lists" of allowable bulk drug substances for compounding (FDA, 2019a).[28] Drug makers may challenge the nomination of a bulk drug substance to the list during a notice-and-comment period, especially if an FDA-approved drug already exists to meet the clinical need. However, until these lists are finalized, FDA's interim policy authorizes facilities to compound using *any* bulk drug substance that has been nominated to the list with sufficient information for FDA to evaluate the substance and that does not raise significant safety concerns (FDA, 2017b,c).

Copycat Drugs

Both Sections 503A and 503B prohibit the compounding of drugs that are "essentially copies" of FDA-approved drug products. However, what FDA considers a copy differs between the two categories of compounding. Section 503A prohibits compounders from compounding "regularly or in inordinate amounts" drugs that are "essentially copies" of FDA-approved drugs. Under Sections 503A and 503B, drug copies do not include compounded formulations that have been changed in a way that the prescriber determines will provide a significant difference for an identified individual patient compared to a FDA-approved drug product. Unlike Section 503A, Section 503B allows copies of FDA-approved drugs to be compounded if the approved drug is on the drug shortage list.[29] The prohibition on compounding copies of FDA-approved drugs ensures that patients do not receive compounded drugs that have not undergone FDA approval when their needs could be met by FDA-approved drugs.

Labeling

Drugs compounded under Sections 503A and 503B are exempt from certain federal labeling requirements. However, Section 503B does require the inclusion of certain label information on compounded drugs, including the statement "this is a compounded drug" (or comparable statements),

[26] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

[27] FDA limitations on the bulk drug substances available to outsourcing facilities for compounding are to prevent outsourcing facilities from growing into manufacturing operations that make unapproved drugs (FDA, 2019a).

[28] List of Bulk Drug Substances That Can Be Used to Compound Drug Products in Accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act. 21 CFR §§ 216 (February 19, 2019).

[29] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

the dosage form and strength, the date the drug was compounded, the expiration date, and storage and handling instructions, among others. If the drug is dispensed or distributed other than for a patient-specific prescription, it must be labeled with the statement "not for resale" or "office use only." For outsourcing facilities, the container for individually stored units of compounded drugs must include a list of active and inactive ingredients, where to report adverse events, and directions for use (Dabrowska, 2018).[30] However, compounded drugs are not required to have labels that mirror FDA-approved versions in the same drug class. For example, if a class of FDA-approved drugs is required to have a boxed warning (the most prominent kind of warning featured on a drug's labeling), a compounded drug containing an active ingredient in that class is not required to carry the same boxed warning (FDA, 2018b).

Interstate Distribution

Section 503A prohibits compounding pharmacies from distributing compounded drugs outside of the state in quantities that exceed 5 percent of the total prescription orders dispensed or distributed by that pharmacy, unless the state has entered into a Memorandum of Understanding (MOU) with FDA.[31] The policy serves to facilitate investigations of complaints related to compounded drugs distributed out of the state where it was compounded, and to prevent inordinate interstate distribution of compounded drugs that is characteristic of drug manufacturing.[32,33] The law does not restrict interstate distribution of compounded drugs from 503B outsourcing facilities.

Regulations Related to Marketing: The Federal Trade Commission and the Consumer Protection Act

Compounded drugs have been promoted through major marketing campaigns in physician offices and pharmacies, as well as by online advertisements. Some of these promotional campaigns have included unsubstantiated claims of safety, disease prevention, and antiaging properties (Patsner, 2008). While the FDCA gives FDA authority to take enforcement action against compounders who produce misbranded drugs (defined as those that

[30] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

[31] See the Federal Food, Drug, and Cosmetic Act § 503A(b)(3)(B)(i). 21 U.S. Code Chapter 9.

[32] A standard MOU has not yet been finalized. A draft form of the agreement, published in 2018, can be found at https://www.fda.gov/media/91085/download (accessed April 13, 2020).

[33] Memorandum of Understanding Addressing Certain Distributions of Compounded Drug Products Between the States and the Food and Drug Administration; Revised Draft; Availability. 83 FR 45631 (September 10, 2018). https://www.govinfo.gov/content/pkg/FR-2018-09-10/pdf/2018-19461.pdf.

make false or misleading claims),[34] oversight of the fairness of commercial advertising of drugs in the United States also falls to the Federal Trade Commission (FTC, 2019). According to FTC's Deception Policy Statement, an advertisement is considered "deceptive" if it contains a statement, or omits information, that is (1) likely to mislead consumers acting reasonably under the circumstances (e.g., misleading price claims, sales of hazardous products or services without adequate disclosures); and (2) is "material," meaning it is likely to affect a consumer's conduct or decision in regard to the product or service (Miller, 1983).

In April 2007, FTC representatives testified to Congress on its actions against sellers falsely promoting compounded bioidentical hormone therapy (cBHT). Specifically, FTC staff searched for online websites claiming that their progesterone preparations were safe and could prevent, treat, or cure serious illnesses, such as cancer and osteoporosis. FTC found 34 websites making such misleading claims and sent warning letters to each seller. FTC has followed up with these companies, identifying 15 that had removed the claims or preparation from their website, and made further enforcement recommendations for those who had not taken corrective action. The testimony also discussed FTC's close partnership with FDA in addressing misleading claims for cBHT sold online (U.S. Senate, 2007). See Box 3-1 for additional information on FTC standards and practices for deceptive advertising.

In October 2007, FTC filed complaints against seven additional online sellers of cBHT, alleging they sold compounded progesterone preparations based on claims without scientific evidence. According to FTC's complaints, the respondents claimed their compounded progesterone creams were:

- Effective in preventing, treating, or curing osteoporosis;
- Effective in preventing or reducing the risk of estrogen-induced endometrial (uterine) cancer; and
- Do not increase the user's risk of developing breast cancer and/or are effective in preventing or reducing the user's risk of developing breast cancer (FTC, 2007).

Since the complaints were issued, six of the sellers have signed consent orders preventing them from making similar unsubstantiated claims in the future (FTC, 2007).

States also may play a role in combating false and misleading advertisements. Recently, Tennessee prevailed in demonstrating that a compounding pharmacy in the state had violated the Tennessee Consumer Protection Act with its cBHT marketing and advertisements. The final ruling concluded

[34] Federal Food, Drug, and Cosmetic Act § 505D(c)(1). 21 U.S. Code Chapter 9.

BOX 3-1
FTC and Deceptive Advertising

FTC standards and practices help determine if an ad is deceptive. Typically, FTC will investigate an ad from the point of view of the "reasonable consumer," examining the advertisement holistically, including its words, phrases, and pictures, to determine the underlying message and implications it conveys to the average consumer. It then compares both "express" and "implied" claims. An express claim is the literal wording of the advertisement, while an implied claim refers to the claim made indirectly or through inference (Miller, 1983). As an illustrative example, "ABC mouthwash prevents colds" is an express claim, while "ABC mouthwash kills cold-causing germs" contains an implied claim that the product will prevent common colds. Although this hypothetical advertisement does not directly claim that the product will prevent colds, it may be reasonable for a consumer to conclude that the product prevents colds by "killing the germs that cause colds." Federal law mandates advertisers to have evidence to support both express and implied claims (FTC, 2006).

When determining whether an advertisement is deceptive, FTC also looks for any omissions or failure to include information that leaves the consumers with a false impression of the product. FTC examines whether an ad's claim would be "material" (e.g., including representations about a product's performance, features, safety, price, and effectiveness) (Miller, 1983) and determines whether an advertiser has sufficient scientific evidence to substantiate claims (FTC, n.d.). Penalties for false advertising depend on the nature of the violation; however, remedies that FTC or the courts have imposed have included (1) cease-and-desist orders; (2) civil penalties, consumer redress and other monetary remedies; and (3) corrective advertising (FTC, 2001a).

that the compounding pharmacy had engaged in deceptive advertising by promoting cBHT as absolutely safe and free from side effects, as well as making claims regarding the benefits of cBHT without adequate support. The pharmacy in question was ordered to pay more than $18 million in damages to the consumers who had used its cBHT preparations.[35]

For consumers to understand the potential risks and benefits of cBHT, it is important that labeling and advertising claims related to compounded drugs be truthful, not misleading, and substantiated with sound evidence. This may be especially true for hormone therapy, since some of the more serious adverse events associated with hormone therapies can take years to

[35] Office of Tennessee Attorney General. 2020. Email from B. Harrell to National Academies staff regarding *State of Tennessee v. HRC Medical Centers, Inc.* legal decision. April 29, 2020. Available through the National Academies Public Access File.

develop, delaying the realization of the true harm of false and misleading advertising (Cirigliano, 2007).

FTC does not offer specific guidance on advertising compounded drugs. It has, however, issued recommendations for advertising dietary supplements that could aid compounders in the development of advertising material. These recommendations call for:

> (1) careful drafting of advertising claims with particular attention to how claims are qualified and what express and implied messages are actually conveyed to consumers; and (2) careful review of the support for a claim to make sure it is scientifically sound, adequate in the context of the surrounding body of evidence, and relevant to the specific product and claim advertised. (FTC, 2001b)

CURRENT CONCERNS WITH FEDERAL REGULATIONS FOR COMPOUNDED DRUGS

Despite the FDAMA's and the DQSA's clarification of compounding's federal regulatory environment, confusion over some aspects of compounding regulation and oversight remain, particularly where both federal and state regulators have overlapping authority.[36] These points of unresolved confusion include the registration of outsourcing facilities, prescription requirement, and pharmacy inspections.

Outsourcing Facility Registration

While Section 503B confers the ability to compound without a patient-specific prescription,[37] the investment required to comply with CGMP requirements may create incentives for facilities to forego voluntary 503B registration with FDA. Thus, compounding pharmacies that distribute drugs without a prescription do so without the commensurate oversight, instead purporting to operate inappropriately under 503A oversight (FDA, n.d.). The exact number of large-scale pharmacies compounding beyond the scope of 503A is unknown, but as of February 2020, only 73 of the tens of thousands of U.S. compounding facilities were registered as 503B outsourcing facilities (FDA, 2020c).[38] In 2016, FDA reported that "in the substantial majority of cases, inspected human drug compounders not registered as outsourcing facilities were compounding at least some of their drugs not in accordance with Section 503A" (FDA, n.d.).

[36] State regulation of drug compounding is discussed later in this chapter.
[37] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.
[38] See Appendix E for additional estimates for 503A and 503 compounders.

FDA has declared its intention to pursue 503A pharmacies operating as outsourcing facilities, commenting that it will focus its oversight efforts on 503A pharmacies that are "large-scale, multistate distributors" (Gottlieb, 2018). FDA also declared plans to facilitate compliance with 503B requirements by directing resources toward preoperational inspections and meetings, enhancing postinspection communications, and conducting more regulatory meetings. In addition, FDA plans to implement more flexible, risk-based CGMP requirements that account for the size and scope of an outsourcing facility's operations as means of lowering the barriers for compounders to register as outsourcing facilities (Gottlieb, 2018). FDA offers in-person and online training geared toward outsourcing facility pharmacists and staff through its Compounding Quality Center of Excellence in an effort to increase understanding of and compliance with the CGMP requirements applied to 503B outsourcing facilities (FDA, 2020a). See Box 3-2 for an additional discussion of concerns regarding large-scale 503A compounding pharmacies.

BOX 3-2
Large-Scale Compounding Operations at 503A Compounding Pharmacies

Large-scale compounding operations are acquiring pharmacy licenses in multiple states and operating under 503A exemptions and requirements (see, for example: Compounding Pharmacy of America, 2020a; University Compounding Pharmacy, 2020; Women's International Pharmacy, 2020). These pharmacies can then maintain a nationwide market and customer base while adhering to the less comprehensive 503A oversight instead of the more rigorous 503B requirements intended to mitigate risks of such large-scale compounding operations with a broader effect on public health.

While these large-scale 503A pharmacies are limited to compounding patient-specific prescriptions, it is unclear what processes they follow to compound these prescriptions. However, given the large number of patients and prescribers these pharmacies serve, it is likely that many identical prescriptions are received. In fact, because several of these large-scale 503A compounders provide patients with options of common compounding bioidentical hormone therapy formulations they offer (see, for example: Compounding Pharmacy of America, 2020b), it is probable that many prescriptions are compounded in bulk rather than individually. This situation provides an opportunity for a repeat of the New England Compounding Center tragedy, in which large batches of compounded drugs are being made without the quality controls for large-scale compounding, and then distributed to a large number of patients across the country.

Prescription Requirement

A second point of controversy is the prescription requirement for 503A compounding pharmacies. The FDCA establishes that producing and distributing compounded drugs without a prescription is only allowed in 503B outsourcing facilities. Section 503A compounding pharmacies, in contrast, require patient-specific prescriptions to dispense compounded drugs.[39] However, some state laws, in conflict with federal law, do allow 503A pharmacies to compound "office stock" without a patient-specific prescription (The Pew Charitable Trusts, 2016).[40] Another complicating factor is that in these situations, the compounder and the prescriber of the compounded drugs may be the same individual, setting the stage for a potential conflict of interest not found in the traditional prescription model in which the prescriber and the manufacturer are two different entities.

Certain health care providers have argued for "office use" compounding in 503A pharmacies for health care providers who need compounded drugs for immediate administration (FDA, 2019f). FDA has maintained its position that 503A pharmacies may not compound for office use, stating that pharmacies that need to keep compounded drugs can obtain non-patient-specific compounded drugs from 503B outsourcing facilities (FDA, 2016c). Further complicating the situation, the House of Representatives Committee on Appropriations has indicated that Congress did not intend to prohibit 503A pharmacies from compounding office stock with the passage of the DQSA, requesting that FDA develop guidance on how these pharmacies may continue this practice while complying with federal law.[41]

Pharmacy Inspections

Inadequate safety inspections remain a third point of contention, particularly related to 503A pharmacies. FDA has the authority to inspect 503A compounding pharmacies, as they are still subject to portions of FDCA regulation, including the prohibition of compounding in insanitary conditions.[42] However, 503A compounding pharmacies are not subject to CGMP requirements or routine FDA inspections, even though they represent the majority of compounding facilities in the United States. However,

[39] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

[40] Office use refers to non-patient-specific compounding that is for the purpose of providing compounded drugs that can be kept on site by hospitals, clinics, or practitioners and can be used when a patient presents with an immediate need for the drug.

[41] U.S. Congress, House of Representatives, Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Bill, 2016, Report 114-205, 114th Cong., 1st sess., introduced in House July 14, 2015, https://www.congress.gov/congressional-report/114th-congress/house-report/205.

[42] 21 U.S.C. § 704(a).

because Section 503A does not require registration with FDA, the agency does not have an inventory of compounders purporting to operate under Section 503A. As a result, FDA often remains unaware of potential issues with compounded drug products or pharmacy facility conditions at 503A pharmacies until it receives a complaint or adverse event report (FDA, 2018c). Based on published calculations, FDA has conducted over 400 inspections and issued more than 150 warning letters since the enactment of the DQSA (Dabrowska, 2018). See Box 3-3 for a brief discussion of illustrative findings from select compounding pharmacy inspections.

PROFESSIONAL STANDARDS OF DRUG COMPOUNDING

There are two primary sources for professional standards of drug compounding: the U.S. Pharmacopeia (USP) and a system of voluntary accreditation.

USP <795>, <797>, <800>

USP is a nonprofit organization that sets standards for the identity, strength, quality, and purity of ingredients used to make drugs. There are three types of compounding standards:

1. USP-NF monographs for bulk drug substances and other ingredients used in drugs, both compounded and manufactured, as well as set standards for identity, quality, purity, strength, packaging, and labeling.
2. USP compounded preparation monographs provide guidance and set quality standards for the process of preparing compounded formulations (USP, n.d.-b). These preparation monographs include formulas, directions for compounding, beyond-use dates, packaging and storage information, acceptable pH ranges, and stability-indicating assays (USP, n.d.-a). USP currently provides more than 175 compounded preparation monographs (USP, 2019).
3. USP also offers eight essential General Chapters that provide overviews of relevant information, procedures, and analytical methods for compounding: USP General Chapters <795>, <797>, <800>, <825>, <1160>, <1163>, <1168>, and <1176> (USP, n.d.-b). Box 3-4 provides more detail about each of those General Chapters.

USP itself does not have regulatory or enforcement authority, but certain USP standards are enforceable under state law (The Pew Charitable Trusts and NABP, 2018). USP standards for compounding were first included in the federal law in Section 503A of the FDCA, which states that,

BOX 3-3
Illustrative Findings from
Select Compounding Pharmacy Inspections

In recent years, the U.S. Food and Drug Administration (FDA) has found numerous compounding facilities to be in violation of some portion of either Section 503A or Section 503B. Below, the findings of several 503A pharmacy and 503B facility inspections performed by FDA are described.

Case 1: The findings of a 2019 FDA inspection of a 503A compounding pharmacy in New York City revealed that several drugs tested did not meet the strength, purity, or quality that the drug was purported to have. One of the compounded preparations tested, a compounded bioidentical hormone therapy (cBHT) formulation of estriol, dehydroepiandrosterone (DHEA), testosterone, and pregnenolone, contained at least 15 percent less estriol, DHEA, and testosterone than the drug was supposed to contain. The inspection also found that there were insanitary environmental conditions and equipment being used at the pharmacy (FDA, 2019c).

Case 2: The 2018 inspection of a 503A pharmacy located in Las Vegas, Nevada, found that the methods used to sterilize cBHT pellets were not sufficient to ensure that the drugs would be sterile. The inspection also found numerous examples of insanitary equipment and poor environmental conditions (FDA, 2018d).

Case 3: A 2018 FDA inspection of a 503B facility in San Antonio, Texas, revealed that aseptic and sterilization processes were not adequately validated to prevent contamination of sterile products. In addition, the inspection found that insanitary equipment was used in the compounding process. The outsourcing facility was also found to have neglected to investigate failures in batches of compounded drugs or quality failures. This facility lacked written procedures for controls to validate identity, strength, quality, and purity of the drugs being produced (FDA, 2018e).

NOTES: A complete registry of similar inspection results can be found at the FDA-maintained website Compounding: Inspections, Recalls, and Other Actions. See https://www.fda.gov/drugs/human-drug-compounding/compounding-inspections-recalls-and-other-actions (accessed May 4, 2020).

BOX 3-4
United States Pharmacopeia General Chapters Related to Compounding

<795> Pharmaceutical Compounding–Nonsterile Preparation contains standards for compounding nonsterile drugs—including process, facilities, equipment, components, documentation, quality controls, and training—to help ensure that medications are safe and effective while reducing the risk of contamination, infection, or incorrect dosing.

<797> Pharmaceutical Compounding–Sterile Preparations describes requirements for sterile compounding, such as training and responsibilities for compounding personnel, facilities, environmental monitoring, storage, and testing of finished preparations.

<800> Hazardous Drugs–Handling in Health Care Settings provides standards and requirements for all health care personnel who come into any contact with hazardous drugs or the environments in which hazardous drugs are handled.

<825> Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging describes the standards and procedures for preparing manufactured radiopharmaceuticals and compounding patient-specific radiopharmaceuticals.

<1160> Pharmaceutical Calculations in Pharmacy Practice describes how to appropriately perform calculations required for compounding and dispensing medications, including quantities of ingredients, dosages, infusion rates, endotoxin load, stability, and expiration dates.

<1163> Quality Assurance in Pharmaceutical Compounding explicates the responsibilities and practices of a robust quality assurance system for compounded preparations.

<1168> Compounding for Phase 1 Investigational Studies provides guidance on compounding investigational drugs for use in phase 1 clinical trials.

<1176> Prescription Balances and Volumetric Apparatus Used in Compounding describes the balances and volumetric apparatuses for measuring drugs and other substances used in compounding.

NOTES: For the complete text of each of these General Chapters, please visit the USP Compounding Standards website. At the time of this report, revised versions of select USP chapters have been published. A discussion of proposed revisions to the published chapters can be found here: https://www.usp.org/compounding/compounding-appeals (accessed April 16, 2020).
SOURCE: USP, n.d.-b.

"compounders must use bulk drug substances and ingredients that comply with the standards of an applicable USP-NF monograph, if a monograph exists, and the USP chapter on pharmacy compounding."[43] While many states have adopted all or parts of the USP General Chapters on drug compounding, allowing for state regulators and inspectors to enforce these quality standards, compounders in some states are not required to comply with USP compounding standards. Compounding pharmacies in states that have not adapted these chapters, or equivalent standards, are not legally required to compound drugs according to these quality measures (see Figure 3-3).

Some state boards of pharmacy have encountered challenges with enforcing USP chapters, as the language of the chapters is sometimes ambiguous regarding what is required versus recommended. Moreover, the degree of enforcement and oversight will vary from state to state based on the resources, expertise, and capacities of each state's board of pharmacy (The Pew Charitable Trusts and NABP, 2018).

A System of Voluntary Accreditation

Compounding pharmacies can voluntarily request accreditation processes to gain third-party validation that could be an attractive selling point to both prescribers and patients. For instance, the Pharmacy Compounding Accreditation Board (PCAB), under the Accreditation Commission for Health Care, has established national quality standards for compounding pharmacies based on industry expert consensus (Springer, 2013).[44] The accreditation process evaluates compliance with the nonsterile and sterile pharmacy compounding standards outlined in USP <795> and USP <797>, respectively, for improved quality (ACHC, 2020). According to pharmacy organization representatives, there are nearly 700 PCAB-accredited pharmacies in the United States, and having this accreditation suggests that compounding composes a larger part of the overall business for those pharmacies (NASEM, 2019).[45] Similarly, The Joint Commission Medication Compounding Certification program assesses a pharmacy's compliance with specific standards for preparation and dispensing of sterile and

[43] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

[44] PCAB was founded by the following pharmacy organizations: American College of Apothecaries, National Community Pharmacists Association, American Pharmacists Association, National Alliance of State Pharmacy Associations, Alliance for Pharmacy Compounding, National Home Infusion Association, National Association of Boards of Pharmacy, United States Pharmacopeia (Springer, 2013).

[45] Also of note, the nearly 700 PCAB-accredited pharmacies represent only a small proportion of all pharmacies that compound. See Appendix E for additional estimates for 503A and 503 compounders.

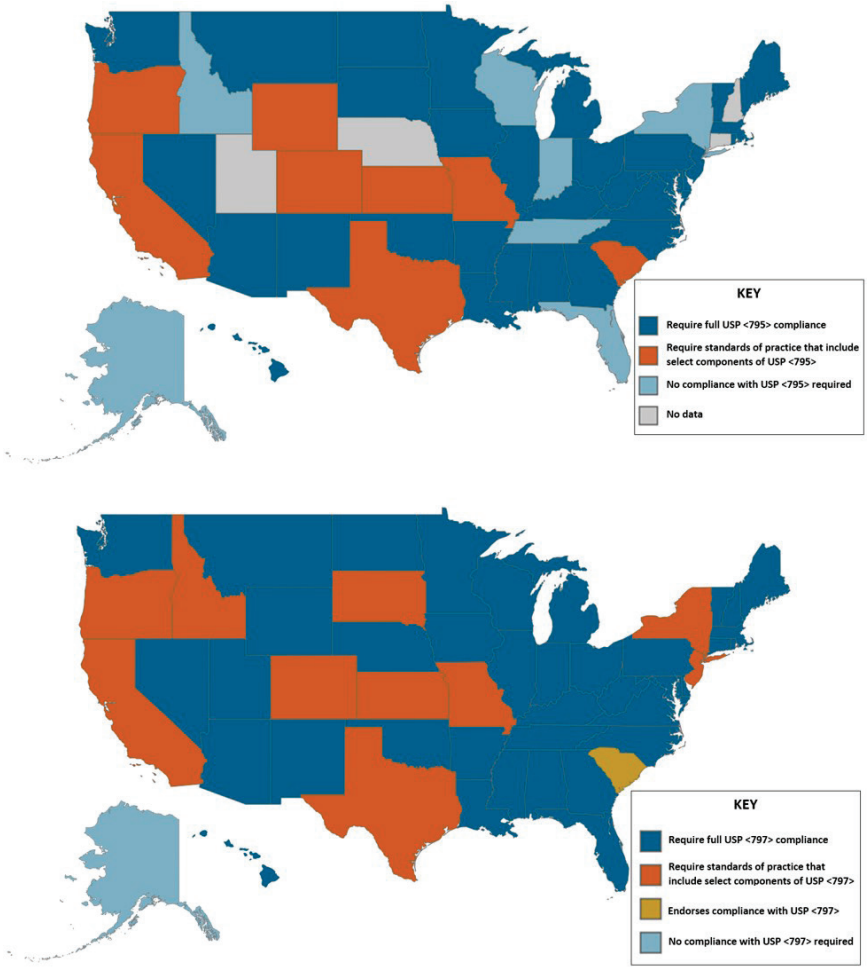

FIGURE 3-3 Variability in state requirements for 503A compounding pharmacy compliance with USP Chapter <795> (top) and <797> (bottom) standards.
NOTES: Maps are based on survey data reported by state boards of pharmacy and collected by the National Association of Boards of Pharmacy, as well as updates from state boards that had pending legislation at the time of data collection. Idaho Administrative Code, Section 27.01.05.100.05; Illinois Administrative Code, Section 1330.640; Code of Maryland Regulations, Section 10.34.19.02; Pennsylvania Code, Section 49.27.601.
SOURCES: NABP, 2018; The Pew Charitable Trusts and NABP, 2018.

nonsterile formulations in accordance with USP <795> and <797> (The Joint Commission, 2019). Starting in the fall of 2019, the Board of Pharmacy Specialties began offering an exam for pharmacists to become accredited in Compounded Sterile Preparations, though the specialty has yet to receive official recognition from the National Commission for Certifying Agencies (Board of Pharmacy Specialties, 2020).

STATE REGULATION OF DRUG COMPOUNDING

In the absence of a strong federal regulatory presence, state entities such as state boards of pharmacy have been the primary regulators of drug compounding practices (Staman, 2012). Indeed, in the NECC case, the Massachusetts Board of Registration in Pharmacy (in a joint operation with FDA) had taken action against the facility before the fungal meningitis outbreak, including issuing a cease-and-desist order to NECC for preparing and distributing compounded drugs without a patient-specific prescription (U.S. House of Representatives, 2012). However, state authorities around the country have taken different approaches to the oversight of compounding pharmacies, leading to substantial variation in the level of oversight and frequency of inspections across states.

Even after the DQSA, the majority of compounding pharmacies remain under the oversight of state entities. Outside of high-risk 503A compounding pharmacies and 503B outsourcing facilities, FDA has maintained that its "aim is to leave the oversight of traditional pharmacy to states" (FDA, 2018a). States face many challenges in regulating and supervising compounding pharmacies, many of which are tied to resource constraints (The Pew Charitable Trusts and NABP, 2018).

Inconsistent Oversight

As noted above, state oversight of 503A compounding pharmacies can be inconsistent. In a 2018 survey update of 43 states, 11 (26 percent) reported they do not require compounding pharmacies to have patient-specific prescriptions in advance of compounding. Although the states reportedly place limitations on this practice (The Pew Charitable Trusts and NABP, 2018), the committee has concerns regarding the state-by-state variability in enforcement of these restrictions.

In addition to in-state oversight, state boards of pharmacy also regulate out-of-state pharmacies that ship compounded preparations into their jurisdictions, a process complicated by the variable compounding standards held by individual states. Not only do states have incongruent quality standards for compounding, but states differ in whether they require out-of-state pharmacies to be in compliance with the receiving state's regulations or those

of the state where the pharmacy is located (The Pew Charitable Trusts and NABP, 2018). This means that preparations compounded under less rigorous standards can still be shipped to a state with more stringent standards.

Similar considerations relate to state inspections. Half of states do not conduct routine inspections of 503A compounding pharmacies, and of those that do, the time between inspections ranges from 1 to 5 years. While best practices recommend that "inspectors of sterile compounding pharmacies should be educated and trained to examine the type of facility they are reviewing," some states have pharmacy inspectors who are not specially trained to review the practice of compounding (The Pew Charitable Trusts and NABP, 2018).

Physician compounding is another area with inconsistent state oversight. Licensed physicians are allowed to compound in a clinical setting under Section 503A,[46] yet tracking and oversight of this practice is not as well established as compounding taking place in a pharmacy. Physician compounding is overseen by state boards of medicine, and most states do not have regulations governing this practice (The Pew Charitable Trusts, 2016).

Efforts have been made to decrease the interstate variability in the oversight of compounding. The National Association of Boards of Pharmacy (NABP) has developed a Multistate Pharmacy Inspection Blueprint Program that provides states with standardized inspection requirements to help ensure consistency in the quality of compounding facilities and processes across states. Currently, 19 states have signed on to this plan (NABP, 2019). FDA has also released a revised draft MOU that will help state regulators to coordinate investigations and corrective actions when compounded medications are shipped across state lines (FDA, 2018f).

Federal–State Coordination

Given the shared federal and state regulatory authority over compounding, some degree of coordination between these levels is to be expected. Section 503B of the FDCA provides FDA with greater oversight of 503B outsourcing facilities than it has for 503A compounding pharmacies. Questions have arisen regarding how state laws or regulations governing compounded drugs should apply when overlap or conflict exists with expanding FDA oversight. Such state compounding laws or regulations could include those regulating sterility testing, adverse event reporting, and compounding for office use (Brown and Tomar, 2016). FDA nominally oversees interstate distribution, but in an effort to increase coordination with the states, FDA has recently awarded a grant to NABP to facilitate information

[46] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

sharing between state regulators and FDA regarding interstate distribution of compounded drugs (HHS, 2019).

Conversely, state laws or regulations might affect a federal compounding regulatory system, as is the case with state regulation of 503B outsourcing facilities. While outsourcing facilities are overseen by FDA, 38 states license or register 503B facilities under various categories, including outsourcing facilities, manufacturers, wholesale distributers, or others.[47] Additionally, while federal law does not require outsourcing facilities to obtain a pharmacy license, some states do, while others prohibit pharmacy licensure of 503B facilities. Such overlapping regulatory schemes can be challenging for facilities seeking to register as 503B distributors (The Pew Charitable Trusts and NABP, 2018).

It is likely that federal-state coordination in compounding regulation will continue to evolve. FDA has invited states to participate in its inspections and recall discussions and has sought to share inspection and enforcement information with state entities (Gottlieb, 2018).[48] The U.S. Government Accountability Office (GAO) published a report in November 2016 on drug compounding that included survey results of state pharmacy regulatory entities. Of 40 states that reported having communications with FDA regarding compounding, 60 percent reported being very or somewhat satisfied with the communication, whereas 23 percent reported being very or somewhat dissatisfied related to delays in response time (GAO, 2016).

Conclusion 3-1

The production, labeling, distribution, and marketing of compounded preparations is regulated at the federal and state levels. However, the widely variable capacities and inconsistencies in oversight, particularly for 503A compounding pharmacies, are a matter of concern.

FINANCIAL ISSUES AND CONFLICTS OF INTEREST

Development, formulation, and appropriate use of prescription drugs requires participation of many different partners and collaborators, including the patient, physician, pharmacist, and pharmaceutical companies involved in synthesizing active pharmaceutical ingredients and manufacturing

[47] These broad categories likely affect the agreement with the data presented in Figure 3-1.

[48] FDA has convened seven intergovernmental meetings with state governments since 2013 (FDA, 2019d).

final products. Each of these roles carries clinical, financial, scientific, ethical, and other responsibilities that may put the physician, pharmacist, or pharmaceutical company executive in conflicting roles or positions.

A conflict of interest exists when professional judgment concerning a primary interest is vulnerable to undue influence by a secondary interest (Thompson, 1993). In the case of the compounded drug market, primary interests include physicians' ethical (and legal) responsibility to provide evidence-based and patient-centered clinical care and compounders' similar responsibility to produce high-quality products for their patients. Thus, there is an expectation that ethically practicing physicians will maintain freedom from financial relationships that could compromise patient trust and lead to potentially inappropriate patient care decisions. According to the American College of Physicians Ethics, Professionalism, and Human Rights Committee:

> The physician must seek to ensure that the medically appropriate level of care takes primacy over financial considerations imposed by the physician's own practice, investments, or financial arrangements. Trust in the profession is undermined when there is even the appearance of impropriety. (Snyder, 2012)

Experience in the pharmaceutical industry has shown that financial relationships can exert particularly strong effects on these primary interests. For example, decades of experience have shown that when physicians have financial relationships with pharmaceutical manufacturers, ranging from accepting meals to accepting research support, those physicians were more likely to prescribe or recommend brand-name drugs being sold by those companies rather than lower-cost generic products or other similarly effective alternatives (Fickweiler et al., 2017). Several systematic reviews have also found potential conflicts of interest in the complementary medicine market. These reviews have found that while these complementary medicines lack rigorous efficacy data, and even though pharmacists often feel that they do not have the adequate knowledge to counsel patients on these therapies, pharmacists are encouraged to sell these complementary medicines because of business interests and profits (Boon et al., 2009; Salman Popattia et al., 2018).

Navigating conflicts of interest—particularly financial conflicts—is a special concern in the context of circumstances involving compounded preparations in which regulatory oversight is limited and variably enforced. Financial conflicts that could affect the compounding market may arise when pharmacists or physicians are responsible for care of the patient but also own a financial stake in the compounded preparations they provide. In fact, a 2016 GAO report found that following the passage of the DQSA,

companies were targeting physicians with proposals to establish compounding operations in the physicians' offices, seeing physician compounding as the best opportunity to increase profits, because physician compounding has less oversight than compounding occurring in a pharmacy (GAO, 2016). Moreover, in the case of cBHT, providers can charge a few thousand dollars or more for these drugs, and may try to justify this cost to patients by citing—without evidence—potential savings on other medications (for high blood pressure, osteoporosis, or depression) or fewer trips to the doctor (Seaborg, 2019). In such cases, it is worth considering to what extent such claims are being driven by the financial conflicts of interest of the provider.

Congress has sought to address financial conflicts of interest through enhanced disclosure. The Physician Payments Sunshine Act (PPSA), originally passed in 2010 as part of the Patient Protection and Affordable Care Act, requires reporting of all payments or gifts of value greater than $10 made to physicians and hospitals by group purchasing organizations and manufacturers of drugs, biologics, and medical devices covered by certain government payers.[49] Notably, these financial relationships are also required to be publicly disclosed.[50,51] The PPSA, though, does not cover the disclosure of payments and financial relationships between providers and compounding pharmacies or outsourcing facilities.

Individuals with financial stakes in clinics and pharmacies that sell cBHT medications and related services have published peer-reviewed articles on the effects of cBHT. Just as those publishing research about drugs going through the FDA approval process need to disclose involvement with or support from commercial entities, so should those reporting studies of compounded drugs. Researchers' disclosure of conflicts of interest in published literature would improve transparency in the research and results obtained.

cBHT Formulations

The formulations for cBHT are described in several locations (e.g., USP-NF), including many pharmacies that develop their own formulations. These pharmacy-developed formulations are often marketed to prescribers (Compounding Pharmacy of America, 2020b; Women's International Pharmacy, 2018). As one study describes, prescriptions were developed based on patient evaluations at the pharmacy with the individualized formulation sent to their doctor for approval (Ruiz et al., 2011). The developer of the

[49] The government payers are Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

[50] Social Security Act § 1128G (42 U.S. Code 1320a-7h).

[51] Payments are recorded at OpenPaymentsData.CMS.gov.

formulation may have a financial holding with a specific formulation, including all excipients, and so may profit from encouraging the use of that formulation.

In addition, anyone may request that an API or excipient have a USP-NF monograph developed. While the sponsor of the request must provide USP with appropriate information and background materials to evaluate the proposed monograph addition (USP, 2016), this action could be perceived as a conflict of interest. As stated in Section 503A of the FDCA, the existence of a USP-NF monograph for a bulk drug substance allows compounders to use that bulk drug substance in compounded preparations under 503A.[52] Because USP-NF monographs do not directly address the safety or effectiveness of the bulk drug substance, requests to add new monographs without such data could be seen as a way for the sponsor, and 503A compounders generally, to market new compounded formulations by diversifying the APIs available to them.

Pharmacists undoubtedly have an important role in patients' use of medications, as supported by the Centers for Medicare & Medicaid Services advocating for pharmacists' ability to prescribe certain drugs in urgent situations (Wachino, 2017). However, the potential for conflicts of interest, real or perceived, increases when the pharmacist both predetermines the prescription and sells the preparation.

Conclusion 3-2

Strengthening federal and state regulatory oversight, as well as requirements for transparency and disclosure of conflicts of interest, could contribute to safer, more effective use of compounded preparations, including compounded bioidentical hormone therapy.

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4

Reproductive Steroid Hormones: Synthesis, Structure, and Biochemistry

Hormones are a diverse class of molecules that influence complex activities throughout the body. They are commonly categorized as peptides and proteins (e.g., insulin), amino acid-derived (e.g., melatonin), or steroids (e.g., estrogen) (Hiller-Sturmhöfel and Bartke, 1998) and are produced in the gonads and adrenal glands, as well as various other tissue and cell types, including those within the placenta and brain (Schiffer et al., 2019). Hormones can function as endocrine (uses the circulatory system to act on distant cells), paracrine (acts on adjacent cells), autocrine (acts at the surface of the cells in which they are produced), or intracrine (acts within the cell) agents (Rubinow, 2018).

Hormones influence different physiological responses by generating cellular signals through their interactions with ion channels on the surface of cells or by binding to and activating a class of proteins called receptors, which can be on the cell surface or inside the cell. A hormone molecule binding to its receptor triggers a cascade of signals in cells that either activates enzymes or causes changes in the expression of the cell's genes. These actions can have a significant effect on biological function and physiological outcomes, including reproduction, sexual differentiation, development, growth, maintenance of the internal environment, organization of motivated behaviors, and regulation of metabolism and nutrient supply (Hiller-Sturmhöfel and Bartke, 1998; Mani et al., 2012; Melmed et al., 2016).

The remaining sections of the chapter will focus on steroid hormones, define what is meant by the term *bioidentical* steroid hormones, and provide a high-level overview of the structure and biochemistry of the hormones commonly used in compounded bioidentical hormone therapy (cBHT)

preparations (Cui et al., 2013; Kleine and Rossmanith, 2016; Kuhl, 2005; Melmed et al., 2016). The chapter will close with a discussion on the variability in the molecular signaling of steroid hormones and its implications on physiological responses.

REPRODUCTIVE STEROID HORMONES

Given the subject of this study, this chapter will focus on the actions and therapeutic effects of reproductive steroid hormones and prohormones,[1] including estradiol (E2), estrone (E1), estradiol cypionate, estriol (E3), dehydroepiandrosterone (DHEA), pregnenolone, progesterone, testosterone, testosterone cypionate, and testosterone propionate.

Definition of Bioidentical Steroid Hormones

Steroid hormones can be classified into four groups: (1) natural hormones found in nature and formulated into drugs without undergoing chemical modifications; (2) hormones native to the body and synthesized from natural precursors; (3) hormones native to the body and synthesized from nonsteroidal precursors; and (4) synthetic and not native to the body (Bhavnani and Stanczyk, 2012). Irrespective of how they are created or synthesized, all steroid hormones are characterized by the various receptors to which they bind throughout the body.

A *bioidentical* hormone is a term that describes a hormone that is chemically and structurally identical to those produced by the human body, with the implication that an identical chemical structure translates to a physiologic response identical to that of the endogenous hormone. Bioidentical hormones may be synthesized from plant or animal sources, or completely chemically synthesized (American Chemical Society and Sociedad Química de México, 1999; Wang et al., 2011), and they are offered as U.S. Food and Drug Administration (FDA)-approved drug products or as preparations that have not undergone FDA approval (Cirigliano, 2007). What is important to remember is that it is the chemical structure of the molecule, and not the originating source, that determines whether a hormone is bioidentical.

Endogenous Source of Bioidentical Hormones

The human body produces all of the naturally occurring, or endogenous, steroid hormones from cholesterol obtained from food sources or produced internally by the body's own cells. Cholesterol is metabolized in a cell's

[1] Prohormones are precursor molecules that the body can convert into the active hormone molecule.

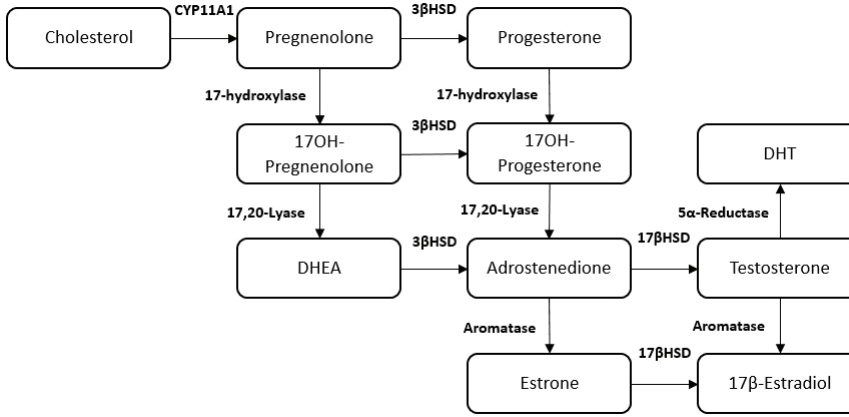

FIGURE 4-1 Biosynthetic pathway of steroid hormones.
NOTES: Figure does not display all intermediate steroids, pathways, or enzymes related to the synthesis of steroid hormones. DHEA = dehydroepiandrosterone; DHT= dihydrotestosterone.
SOURCE: Rubinow, 2018.

mitochondria to generate the steroid hormone pregnenolone. Further metabolism of pregnenolone through a series of enzymatic steps gives rise to all of the biologically active steroid hormones (Melmed et al., 2016) (see Figure 4-1).

Exogenous Sources of Bioidentical Hormones

Exogenous source material, including plants, must be processed chemically to create bioactive hormone products that the human body's endogenous hormone receptors can recognize. Plants, for example, do not produce cholesterol. Rather, they produce related chemicals known as plant sterols that can be converted chemically through laboratory-based enzymatic processing into steroid hormone products (see Figure 4-2).

Regardless of whether the bioidentical steroid hormone is produced endogenously or exogenously, it is the structure of the hormone and the way in which it is metabolized that determines its biological action. This point is critical to understanding the effects of steroid hormones.

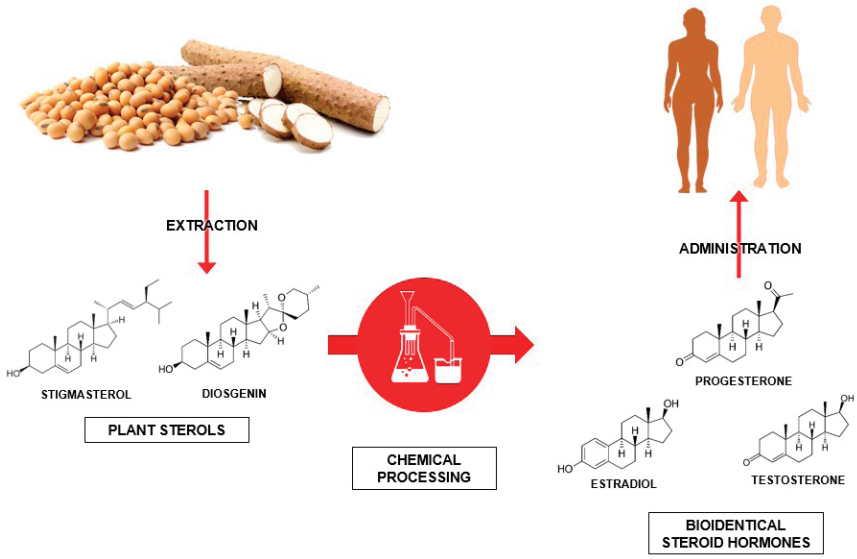

FIGURE 4-2 Production of bioidentical hormones from plant-produced compounds. SOURCES: American Chemical Society and Sociedad Química de México, 1999; MaskaRad, 2018, Stock Illustration ID: 957444020; Popovaphoto, 2015, Stock Illustration ID: 498946090; YuanruLi, 2018, Stock Illustration ID: 916334012; Wang et al., 2011.

Conclusion 4-1

Use of the term bioidentical *is a source of confusion.* Bioidentical *means that the hormone's chemical structure is identical to that of a hormone occurring naturally in the body, and consequently implies its biologic activity is identical to that of a hormone occurring naturally in the body. Many patients believe that* bioidentical *means that plants are the source of the hormones, however, it is the chemical structure and not the source that determines whether a hormone is bioidentical. Furthermore, bioidentical hormone medications that have plant sources and are called* natural *are, in fact, chemically modified in the laboratory before they are provided to a patient.*

STRUCTURE AND BIOCHEMISTRY OF HORMONES COMMONLY FOUND IN COMPOUNDED BIOIDENTICAL HORMONE PREPARATIONS

The structure and biochemistry of steroid hormones commonly used in compounded preparations are described below.

Estrogens

Estrogens—estrone (E1), estradiol (E2), and estriol (E3)—are the predominant female sex hormones, produced primarily in developing follicles in the ovaries. E1 can be converted to E2, E2 can be converted to E1, and within the placenta of a pregnant woman, both E1 and E2 can be converted to E3. Estrogen production increases through puberty and the reproductive years and diminishes as ovarian follicles decrease with age, ultimately falling to low levels during the menopause transition and postmenopausal period. Estrogen production can also occur in male testes and act to regulate gonadal development and spermatogenesis. See Figures 4-3, 4-4, and 4-5 below for the chemical structures of estrone, estradiol, and estriol.

Estrone (E1)

Ovaries are the main source of E1. E1 is a minor hormone in the female reproductive cycle, though it plays a larger physiological role following menopause. Estradiol biosynthesis can occur through a reduction of E1 by 17-beta-hydroxysteroid dehydrogenase (HSD) enzymes.

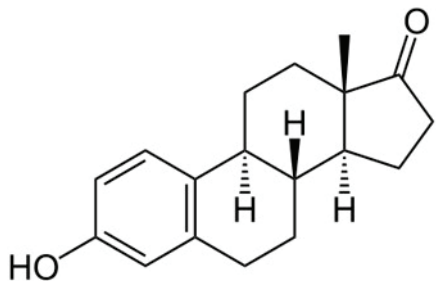

FIGURE 4-3 Chemical structure of estrone (E1).

Estradiol (E2)

Ovaries are the main source of E2. It is also formed by aromatization of testosterone or synthesized by estrone's reduction by 17β-hydroxysteroid dehydrogenase enzymes in tissues outside of the gonads. E2 is a potent estrogen that plays a dominant role in nonpregnant and premenopausal women's development and the regulation of reproductive cycle. The synthesis of E2 is controlled by enzymes called aromatases, which are expressed widely throughout the body and are either activated or inhibited by other hormones or local tissue factors, adding a layer of complexity to the control of E2 production.

Estradiol cypionate is a naturally occurring hormone that is the ester form of E2. In its activated complex, it promotes the transcription of genes involved in the female reproduction system and in producing secondary sex characteristics. Estradiol cypionate can also serve as a prohormone that the body converts readily into the endogenous form, estradiol (NLM, 2020a).

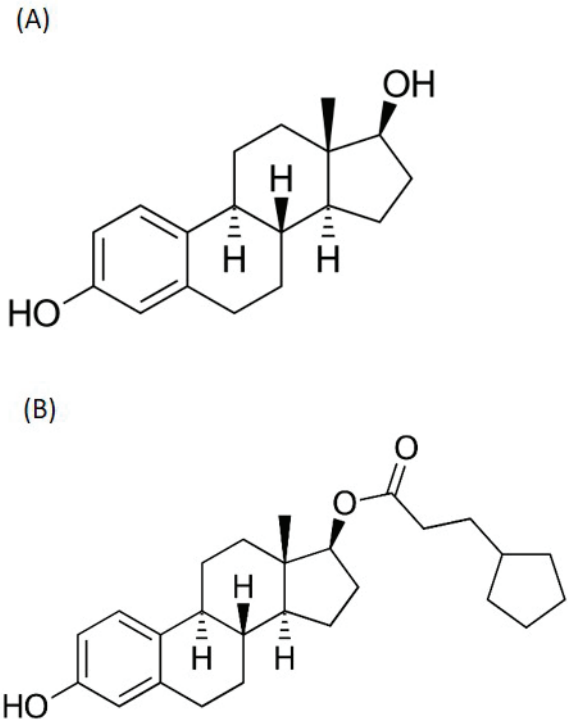

FIGURE 4-4 Chemical structure of (A) estradiol (E2) and (B) estradiol cypionate.

Estriol (E3)

Estriol (E3) is derived from E1 and E2 and is primarily synthesized within the placenta during pregnancy. It is a far less potent estrogen than E2, and with little circulating in nonpregnant women, it serves as a minor female sex hormone (Cui et.al., 2013; Keller, 1974). Though considered to be a relatively weak estrogen, E3 is often included in some of the most commonly compounded formulations of estrogens (e.g., Bi-est, Tri-est).

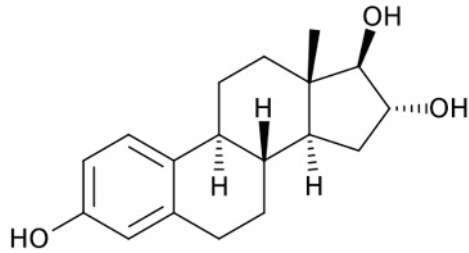

FIGURE 4-5 Chemical structure of estriol (E3).

Pregnenolone

Pregnenolone (P5), is a major precursor of most steroid hormones, including the androgens, estrogens, progestogens, and adrenal steroids (see Figure 4-6). P5 is a neurosteroid, meaning that it is expressed in the brain and can act locally to acutely regulate neuronal function (Ratner et al., 2019).

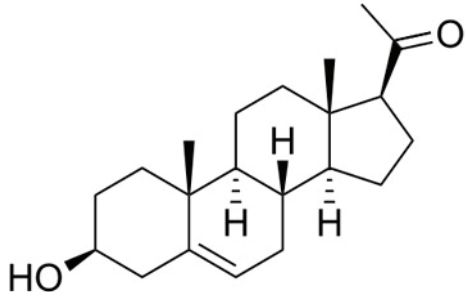

FIGURE 4-6 Chemical structure of pregnenolone.

Progesterone

Progesterone, similar to pregnenolone, is a neurosteroid and precursor for steroid hormones. Progesterone's major source of production comes from the corpus luteum cells that form after ovulation, but it is also secreted by the adrenal glands and placenta. Following menopause, progesterone levels are low. Because of its ability to prevent excessive growth of the uterine lining—a precursor to endometrial cancer—progesterone is often formulated into hormone preparations to biochemically balance the effects of estrogen therapy in postmenopausal women with an intact uterus. (See Figure 4-7 for the chemical structure of progesterone.)

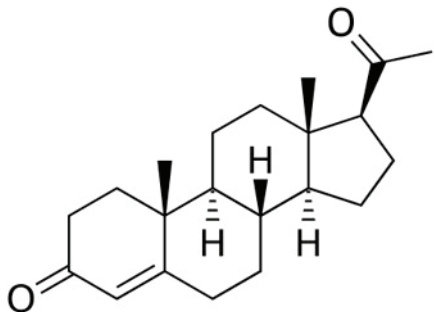

FIGURE 4-7 Chemical structure of progesterone.

Testosterone

Testosterone, Testosterone Cypionate, and Testosterone Propionate

In men, testosterone is an androgen that is synthesized predominantly in the testis from cholesterol through the intermediate DHEA. In premenopausal women, the adrenals and ovaries are the key sources that contribute to circulating levels of plasma testosterone. In postmenopausal women, testosterone is almost exclusively derived from nonovarian tissues.

Testosterone is a potent androgen, and it plays a major role in the development of the male reproductive system and the sexual health of both men and women. Other forms of testosterone, such as testosterone cypionate and testosterone propionate, are also used in compounding. Testosterone cypionate and testosterone propionate are prohormones that the body converts to testosterone (NLM, 2020b). These two forms of testosterone may be useful in compounding because of their differing solubilities. (See Figure 4-8 for the chemical structures of testosterone, testosterone cypionate, and testosterone propionate.)

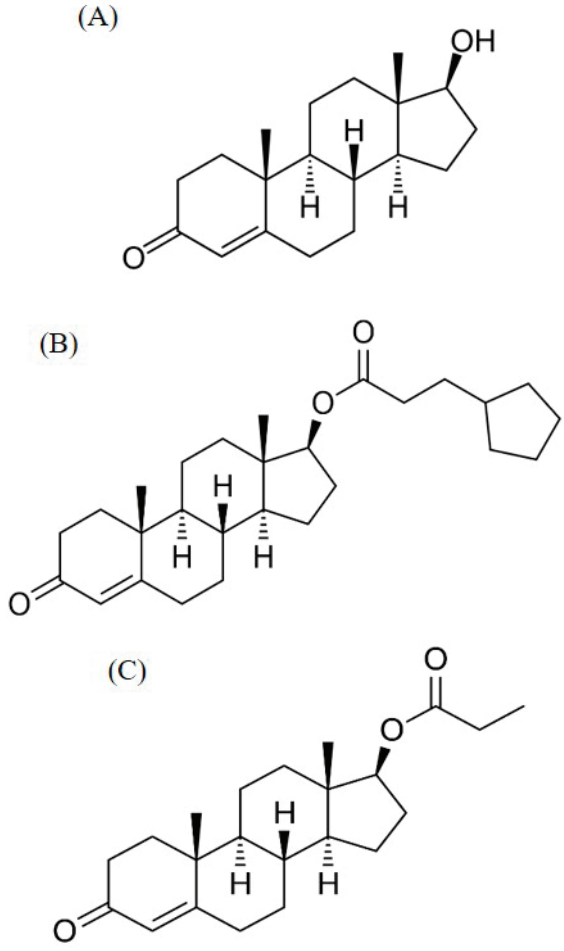

FIGURE 4-8 Chemical structure of (A) testosterone, (B) testosterone cypionate, and (C) testosterone propionate.

Dehydroepiandrosterone

DHEA is an endogenous hormone produced in the adrenal glands and brain. In addition to its own role as a bioactive hormone and neurosteroid, circulating DHEA serves as an important precursor for estrogens and testosterone in postmenopausal women (see Figure 4-9).

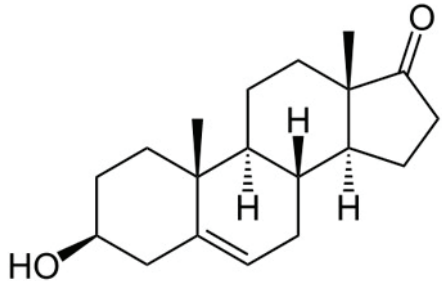

FIGURE 4-9 Chemical structure of dehydroepiandrosterone (DHEA).

STEROID HORMONE SIGNALING

A hormone's unique chemical structure has direct implications for its resultant biologic activity. This activity, including biological functions and physiological outcomes, results from a complex signaling processes. The sections below provide a brief and limited discussion of select aspects of this complexity.

Types of Signaling Mechanisms

There are two general types of steroid hormone signaling, classical and rapid (Belfiore and LeRoith, 2018; Kampa et al., 2008; Kleine and Rossmanith, 2016; Schwartz et al., 2016). In classical mechanisms of hormone action, hormones cross through the plasma membrane and directly bind to and act through intracellular nuclear receptors to regulate transcription of thousands of genes.[2] Rapid steroid hormone signaling occurs through steroid receptors residing in the cell membrane, which when activated by hormones, can initiate downstream signaling to stimulate enzymes, amplify effects of other activated receptors, or directly influence the transcription of various genes. Steroids can also activate cell signaling by binding to nonsteroid membrane receptors, such as the epidermal growth factor receptor, or by binding to ion channels, which include calcium and potassium channels.

[2] Ligand-independent activation of steroid hormone receptors can also occur. Certain steroid hormone receptors can tether to other proteins/transcription factors to bind indirectly to DNA at hormone response elements to affect gene expression (Rubinow and Schmidt, 2018).

Sources of Variance in a Steroid Signal

Multiple Forms and Locations of Steroid Receptors

Steroid receptors exist as multiple isoforms—structurally varied products of the same gene. For example, there are two isoforms of the progesterone receptor for progesterone (Singhal et al., 2017); two isoforms of the androgen receptor (Liegibel et al., 2003); and two forms of the estrogen receptor—ERα and ERβ—are coded for by two separate genes, and owing to alternative splicing events, yield multiple associated isoforms (Yaşar et al., 2017). Steroid receptor isoforms, when bound to their respective steroid hormones, can produce different tissue-specific gene expression patterns and often mediate distinct functional effects. Adding to this complexity, additional diversity can be introduced through posttranslational modifications of receptor isoforms (Faus and Haendler, 2006).

Active Metabolites

The metabolism of steroids can produce other active hormone products with additional mechanisms of action. For example, progesterone is metabolized to produce the neurosteroid allopregnenolone, which acts to modulate the activity of the γ-amino butyric acid (GABA) receptor in the central nervous system. Other active metabolites of progesterone are also found in the brain and produce different effects on excitatory and inhibitory neurotransmitter receptors. In addition, because most enzymes involved in steroid hormone metabolism have been located in the brain, it is suggested that many "parent" steroid hormones (e.g., progesterone, estradiol, and DHEA) may also function as neurosteroids (Porcu et al., 2016).

Coregulators

There is substantial variability in the biological actions and outcomes of steroid hormones. This variability is best illustrated by their interactions with a broad spectrum of protein partners, known as hormone coregulators (Wang et al., 2016), to produce biological effects. For example, there are roughly 350 different coregulatory proteins—coactivators and coinhibitors—that bind to steroid receptors to determine whether genes are turned on or off (Lonard and O'Malley, 2012). Adding complexity to the situation, these coregulatory proteins often combine in groups, and the effect of each individual coregulator within that group is determined by specific chemical modifications to that protein (e.g., phosphorylation or methylation) (Lonard and O'Malley, 2007).

In addition, coregulatory proteins exist in a tissue-specific fashion and are highly context dependent. These features enable estrogen-like compounds called selective estrogen receptor modulators (SERMs) to act as an estrogen agonist (activating biological responses) in some tissues, such as in bone and the heart, and an antagonist (blocking biological responses) in others, including the uterus and breast, depending on the coregulator profile in the cells (Wardell et. al., 2014).

Implications of Signaling Variance for Physiological Responses

One of the confounding factors that makes it difficult to predict how a given mixture of hormones will affect various physiological processes in the body is that the affinity of a hormone for its receptor—the strength with which it binds to that receptor—does not necessarily determine either the potency of the effect or even the direction of its action (Salahudeen and Nishtala, 2017). Further complicating the assessment of receptor affinity is the extraordinary variability of reported findings based on the source (endogenous versus exogenous) (Fuentes and Silvera, 2019) and the tissue or the cell line used to measure receptor binding (Yaşar et al., 2017). In addition, a given hormone's binding partners, particularly the coregulators (as noted above), exist in different concentrations in different tissues, producing tissue-specific effects (Smith and O'Malley, 2004). Similarly, the exact mix of steroid hormones present in a given tissue or cell can affect the activity of the individual hormones in that tissue or cell (Uht et al., 1997). A major source of variability in hormone signaling is the genomic context, resulting in variation in the structure and activity of hormone receptors and the enzymes involved in biosynthesis of the steroid hormones themselves (Fuentes and Silvera, 2019). Therefore, the resulting differences in levels of steroid hormones and receptor actions must also be considered in determining the potential benefits and drawbacks of a particular mix of hormones (Ferrell et al., 2005).

It is also important to recognize that hormones within a given class are not going to produce similar effects on all tissues. For example, medroxyprogesterone acetate is a progestogen but has biological effects that diverge from those of progesterone (Frye, 2013; Nilsen and Brinton, 2003). These differences might translate into different effects on brain and estrogen-sensitive tissues such as breast and uterus. In a similar manner, the genomic effects of conjugated equine estrogens—hormone ingredients in FDA-approved drug products—are not identical to those of E2 (Wroolie et al., 2011). Finally, hormone levels tell only part of the story, meaning, they do not permit inferences about tissue levels based on local metabolism nor about cellular effects of those levels in a given tissue (Fuentes and Silvera, 2019; Smith and O'Malley, 2004).

In summary, the overall effects of steroids are highly context dependent, and they are affected by an individual's genetic background, current steroid milieu, and prior exposure. The diverse and dynamic signaling produced by steroid hormones emphasizes the need for preclinical and clinical evaluation that would identify potential beneficial and adverse health effects using the specific mixture of hormones that is to be used to treat patients.

Conclusion 4-2

Circulating hormone levels are not necessarily predictive of biological activity because steroid hormones, including those used in compounded bioidentical hormone therapy preparations, produce highly variable responses that are dependent on a number of factors, including genetic background, prior exposure to steroid hormones, and environmental and lifestyle factors.

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5

Compounded Bioidentical Hormone Preparations

Medications containing steroid hormones are prescribed frequently to treat symptoms associated with the normal age-related decline in circulating hormone levels. This chapter will provide an overview of compounded bioidentical hormone therapy (cBHT) preparations, including a description of their common formulations (e.g., common active and inactive ingredients), formulation methods, quality testing, and labeling. This chapter will also describe features that may affect the quality of the cBHT preparations and highlight important variations between compounding settings (i.e., 503A compounding pharmacies and 503B outsourcing facilities). Where relevant, this chapter will discuss FDA-approved bioidentical hormone products and commercial drug manufacturing facilities to provide relevant comparisons and contrasts between formulation procedures and quality testing.[1]

For the purposes of this report, the committee maintained a focus prioritized on 10 hormones (7 unique hormone substances and 3 salt forms) that were of interest to the U.S. Food and Drug Administration (FDA). These hormones include estrone (E1), estradiol (E2), estradiol cypionate (Ec), estriol (E3), dehydroepiandrosterone (DHEA), pregnenolone (P5), progesterone (P4), testosterone (T), testosterone cypionate (Tc), and testosterone propionate (Tp). For the purposes of this chapter, the committee will focus its discussion

[1] As a result of the minimal oversight of the compounding process, cBHT preparations are not produced with the same level of quality assurance as FDA-approved products, and they are not required to demonstrate safety and effectiveness in clinical trials before being dispensed to a patient (Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9). See Chapter 3 for an overview of the regulation and oversight of compounded preparations.

on *bioidentical* compounded formulations and, where relevant, *bioidentical* FDA-approved products.[2] However, certain cBHT preparations contain hormones not available in FDA-approved products.

cBHT PREPARATIONS

Potential Variances Between Preparations

Unlike with FDA-approved hormone products, the process of formulating a compounded prescription is entirely compounder specific. That is, the content and quality of the final preparation depends completely on what is described in the Master Formulation Record (MFR) as chosen or described by the compounder.[3,4] Compounder-specific factors that may influence quality and performance of the final preparation include the choice of active and inactive ingredients, ingredient testing, available compounding equipment, compounder skill, quality systems, facility cleanliness, and environmental controls. Per United States Pharmacopeia (USP) standards, once completed, the compounded preparations should undergo an abbreviated release inspection that should at a minimum include a visual inspection of the formulation, but it may also include quality checks developed and reviewed solely by the compounder (USP, 2012, 2014).[5]

While important, the recommended postcompounding inspection process is superficial, in that these steps do not ensure that the compounded preparation contains the purported amount of active ingredient or can deliver the active ingredient to the patient and the site of action. Because of these limitations, different compounders may use different processes to compound an identical prescription, and as a result, cBHT preparations ordered with identical prescriptions and labeled with the same name will

[2] As Chapter 4 noted, a *bioidentical hormone* is a term that describes a hormone that is chemically and structurally identical to those produced by the human body, with the implication that an identical structure translates to an identical physiologic response as endogenous hormones.

[3] As discussed in Chapter 2, a compounder can begin to prepare the patient-specific cBHT preparation as described by the prescription (or clinic order for 503Bs) when an MFR and a compounding record are available.

[4] MFRs are an important component of quality control during the formulation of a drug. If a compounding record deviates from what is written in an MFR without proper documentation for such a change, it is a breach in the quality control that aims to provide patients with consistent formulations of their prescription. As of April 2020, MFRs are only required for certain types of compounding, though similar documentation is also required in current good manufacturing practice regulations. See Written procedures; deviations. 21 CFR 211.100 (April 1, 2019).

[5] As discussed in Chapter 3 of this report, USP itself does not have regulatory or enforcement authority, but certain USP standards are enforceable in some states under state law.

likely vary between compounders. Indeed, FDA has received adverse event reports that reveal harmful variations in compounding (FDA, 2020a; see Chapter 7).

Inadequate Labeling Requirements

Labels for compounded preparations are not required to provide guidance for patients about safe use.[6] This is in contrast with requirements for FDA-approved hormone products to provide labeled instructions for patients on the proper use and storage of the product and warnings about possible risks.[7] For 503A compounding pharmacies, the decision to provide labels for compounded preparations is up to the compounder. As a result, and as presented at the study's open session meetings, dispensed cBHT preparations often do not include the boxed warnings, warnings, contraindications, and detailed instructions for use similar to those included with FDA-approved hormone product labeling, despite containing the same active ingredients (NASEM, 2019c). (See Box 5-1 and Table 5-1 for additional discussion on labeling of FDA-approved hormone products.) Although the federal statutes establishing 503A and 503B compounders specifically exempted them from federal labeling provisions on adequate directions for use,[8] there is no clear clinical rationale for excluding information on the potential risks associated with the use of hormone medication, particularly for those that contain estradiol and testosterone.

Inadequate Data Collection

In addition to concerns related to labeling, there are also concerns related to data collection. Specifically, once an MFR is created, there is no central registry where the MFR must be submitted, and there is no requirement for independent outside review, as is the case for FDA-approved products. Unlike with FDA-approved products, compounded preparations do not have a National Drug Code and are not listed in any conventional shared drug product database. In contrast, basic characteristics of FDA-approved products, including active ingredients, strength, and dosage form, are described in multiple public databases, including the *Orange Book* (FDA, 2020b), RxNorm (NLM, 2019), International Nonproprietary Names (WHO, 2018), and others. This further underscores that compounded preparations are unique to the compounder that prepares them,

[6] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

[7] Requirements on content and format of labeling for human prescription drug and biological products. 21 CFR § 201.56 (December 4, 2014).

[8] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

BOX 5-1
Labeling of FDA-Approved Hormone Products and Boxed Warnings

All FDA-approved products must contain labeling intended to help the patient use the product safely and to understand the potential risks. The information most relevant to patients detailed in this labeling includes contraindications, warnings and precautions, adverse reactions, drug interactions, how the product is supplied, storage and handling requirements, and patient counseling information.* Importantly, the listed ingredients on the labels can be tracked to USP monographs, and sometimes to a Drug Master File (DMF) and the Inactive Ingredient Database, to get more information about the specific active and inactive ingredients contained with the medication. If a supplier-specific ingredient is used, the actual ingredient supplier can be found and queried if necessary. Medication Guides are also available for testosterone products dispensed to patients (FDA, 2019c). Medication Guides are detailed instructions that teach patients how to use the FDA-approved product most safely and effectively, and provides information to help patients avoid serious adverse events (FDA, 2019c).

All estradiol (Stefanick, 2005) and topical testosterone gel (FDA, 2015) FDA-approved products carry boxed warnings in their labeling (see Appendix H for an example of a boxed warning). For estradiol products, the boxed warnings inform the patient about the risks of endometrial cancer, cardiovascular disorders, breast cancer, and probable dementia (Stefanick, 2005). For testosterone, the warnings include the risks of secondary exposure to testosterone and the risks of virilization in children and health care providers that are secondarily exposed (FDA, 2015). Progesterone does not have boxed warnings. See Table 5-1 for a select listing of FDA-approved products and availability of medication guides and boxed warnings.

* Requirements on content and format of labeling for human prescription drug and biological products. 21 CFR § 201.56 (December 4, 2014).

TABLE 5-1 FDA-Approved Drug Products and Availability of Medication Guides and Boxed Warnings

Hormone	Medication Guides	Boxed Warnings
Estradiol	No	Yes
Progesterone	No	NA
Testosterone	Yes	Yes

NOTE: NA = no applicable boxed warning for this active ingredient.

SOURCES: Committee generated, using information from NLM, 2020a.

and that for identical prescriptions, the final compounded preparations may differ between compounding establishments.

Conclusion 5-1

Currently, compounded bioidentical hormone therapy preparations are not adequately labeled. Missing information includes, but is not limited to, a description of the preparation's instructions for use, contraindications, potential adverse effects, boxed warnings, and the identity of the person and company responsible for a compounded preparation's quality and safety. This lack of information undermines safe and effective use by patients and prescribers.

TYPES OF cBHT PREPARATIONS

A wide variety of cBHT dosage forms are dispensed to patients, and because of a lack of registries and surveillance of use, it is difficult to obtain specific estimates for the number of available forms of cBHT preparations. To begin to describe the breadth of cBHT preparations dispensed by compounders, the committee found it necessary to compile its own list of cBHT preparations, drawing on available resources.[9] This list presents only a small sample of the universe of cBHT preparations and at best provides a snapshot and limited description of available cBHT preparations. Indeed, in November 2019, during an open session presentation to the committee, Dr. Gina Besteman, Director of Compounding and Dispensing at Women's International Pharmacy, stated that her 503A pharmacy has "compounded over 149,000 unique hormone formulations using fewer than 10 hormones" (NASEM, 2019a).

[9] Resources included peer-reviewed literature on use of cBHT (e.g., IJPC, 2018), cBHT preparation adverse event reports (FDA, 2018a, 2020a), information provided by compounding practitioners (see Public Access Folder), recent biannual outsourcing facility preparation reports (FDA, 2019a), and online marketing information from compounding pharmacies.

Available Dosage Forms and Routes of Administration

To support the committee's research efforts, Reed Smith LLP submitted a briefing document that contained a list of common cBHT dosage forms.[10] Although this list may not be comprehensive, it describes at least 32 different types of dosage forms of cBHT formulations. In contrast, there are only 13 FDA-approved bioidentical hormone therapy dosage forms available (see Table 5-2).

Of the 10 hormone ingredients of focus for this report, all are available in cBHT preparations except for estradiol cypionate.[11] Table 5-3 provides a summarized list of the different dosage forms available for single active ingredient cBHT preparations, as identified by the committee in their review, and compares them to available dosage forms of FDA-approved single active ingredient BHT products. In summary, the committee found that the single ingredient cBHT preparations are available in a wide variety of dosage forms and strengths, while comparatively there are fewer FDA-approved hormone products available for each of the routes of administration. For example, there are at least 13 different cBHT progesterone dosage forms, including oral (capsule, capsule sustained release, lozenge, oil, tablet), topical (cream, gel, solution, spray), injection (oil, pellets, suspension), rectal (enema), and vaginal (capsule, suppository) preparations, as compared to four different FDA-approved BHT progesterone dosage forms, including oral (capsule), topical (gel), injection (solution), and vaginal (insert). Furthermore, estriol cream and pellets containing estradiol or progesterone only exist as compounded preparations.

Conversely, there is no compounded estradiol or testosterone patch, testosterone film, or estradiol ring, perhaps a result of the complexity of manufacturing these FDA-approved dosage forms (FDA, 2018b, 2019d). Of the 10 hormone ingredients of focus for this report, only 3—DHEA, estriol, and pregnenolone—are not available as injections or implants. The three hormone salts, estradiol cypionate, testosterone cypionate, and testosterone propionate, are water insoluble and are found almost exclusively in depot oil-based injection products. These three preparations are not commonly found in other types of cBHT dosage forms, and as such are not listed in the summary Table 5-3 below. In addition, estrone and pregnenolone were only ever combined with at least one other active ingredient in the cBHT formulations found, and therefore, are also not included in Table 5-3.

[10] Reed Smith LLP is a law firm that represents a coalition of 503B outsourcing facilities, that at the time of this report, incudes Belmar Pharmacy; Fagron North America, which includes Fagron Inc., Humco, B&B Pharmaceuticals; AnazaoHealth Corporation; Women's International Pharmacy; BioTE Medical; and Carie Boyd's Prescription Shop.

[11] At the time of this report, the FDA *Orange Book* does include an FDA-approved estradiol cypionate 5 mg/mL injection (Depo-estradiol) product, which may or may not be related to the inability to find a corresponding cBHT preparation.

TABLE 5-2 Summary of Dosage Forms Available for FDA-Approved Bioidentical Hormone Products and Compounded Bioidentical Hormone Preparations

Dosage Form Available	FDA-Approved BHT Drug Products	Compounded BHT Preparations
Oral	Capsule • Powder-filled • Oil-based Tablet	Capsule • Powder-filled • Lactose-filled • Semi-solid-filled • Oil-filled Tablet triturate Troche and mini troche • Soft • Hard Buccal tablet Soft linguet Liquid (syrup, suspension, emulsion) Sublingual drop (oil)
Vaginal	Gel Cream Insert • Extended release Tablet	Suppository/insert • Water soluble • Lipid-soluble Cream Solution (Poloxamer, etc.)
Topical/ Transdermal	Gel • Metered Films, extended release Spray Metered solution	Creams Gels Microemulsion gels Lotions • Clear • Opaque • Aqueous • Nonaqueous Suspensions
Injection	Oils	Aqueous Nonaqueous (e.g., sesame oil, castor oil, grapeseed oil, cosolvents)
Nasal	Gel, metered	Drop Spray Solution Suspension
Rectal	No FDA-approved option	Enema • Gel • Suspension • Emulsion
Implant	Pellet	Pellet

NOTE: The classification of dosage forms available in FDA-approved products has been adapted from the original table submitted by Reed Smith LLP to mirror the terminology used in the FDA *Orange Book*.

SOURCE: Reed Smith LLP, 2019.

TABLE 5-3 Available Dosage Forms for Single Active Ingredient cBHT Preparations and FDA-Approved BHT Products

Dosage Form	Hormones									
	Estradiol		Estriol		Progesterone		Testosterone		DHEA	
	Preparation									
	C	M	C	M	C	M	C	M	C	M
Capsule	✓	✓	✓		✓	✓	✓		✓	
Capsule SR					✓					
Cream	✓	✓	✓		✓		✓		✓	
Enema					✓					
Film/Patch		✓						✓		
Gel	✓	✓	✓		✓	✓	✓	✓	✓	
Injection	✓					✓				
Insert/Ring	✓	✓				✓			✓	✓
Lotion							✓			
Lozenge	✓				✓		✓			
Oil					✓					
Ointment	✓		✓				✓			
Pellet	✓				✓		✓	✓		
Solution	✓				✓		✓	✓	✓	
Spray		✓			✓		✓			
Suppository	✓				✓				✓	
Suspension					✓					
Tablet	✓	✓			✓					
Total	11	7	4	0	13	4	9	4	6	1

NOTES: C = cBHT preparations from 503A and 503B pharmacies; M = manufactured FDA-approved product; SR = sustained release. The classification of dosage forms available in FDA-approved products has been categorized to mirror the terminology used in the FDA *Orange Book*. Table does not include information for estrone, pregnenolone, estradiol cypionate, testosterone cypionate, or testosterone propionate. This table does not include combinations of active ingredients.

SOURCE: FDA, 2020b.

Available Doses

For each of the dosage forms listed in Table 5-3, the compounding process generates preparations of varying strengths, adding to the number of total possible cBHT preparations available for use. For example, in considering formulations with single and multiple active ingredients, the

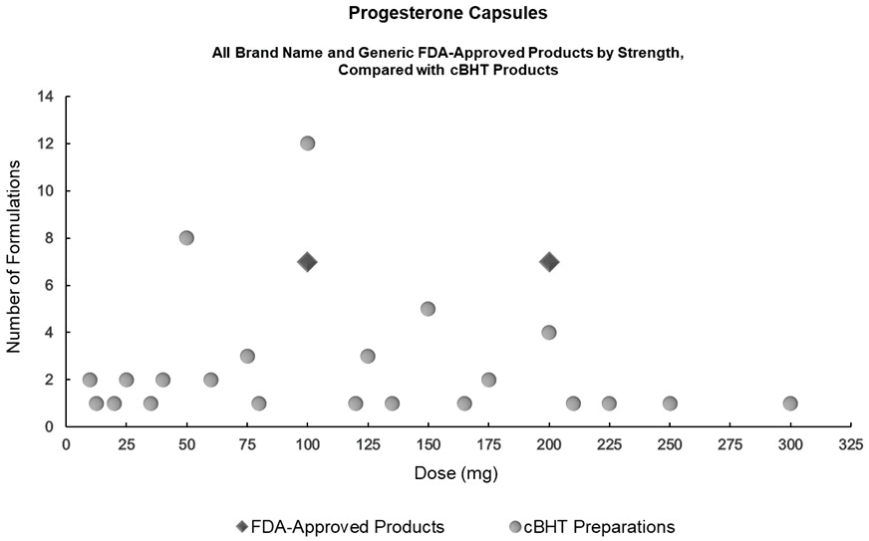

FIGURE 5-1 Comparing the strength of various compounded progesterone capsule formulations to two FDA-approved capsule strengths.
SOURCES: Committee generated, using information derived from peer-reviewed literature on the use of cBHT (e.g., IJPC, 2018), cBHT preparation adverse event reports (FDA, 2018a, 2020b), information provided by compounding practitioners (NASEM, 2019a,b,c), recent biannual outsourcing facility preparation reports (FDA, 2019b, 2020b), and online marketing information from compounding pharmacies.

committee identified hundreds of different formulations and strengths for cBHT preparations (see Appendixes F and G).[12]

To serve as an illustrative example, Figure 5-1 above compares the variety of progesterone capsule strengths against the two FDA-approved capsule strengths. The preparations with low doses of progesterone pose a clinical concern: low dose progesterone has not been found to protect the endometrium and reduce the risk of endometrial cancer induced by unopposed estrogen (Stute et al., 2016). At the committee's open session meeting in November 2019, invited panelist, Dr. Pamela Smith (Center for Personalized Medicine), described these low doses of progesterone as ineffective and something she would not prescribe (NASEM, 2019b). Nonetheless, these doses are still available and marketed to patients for use. In

[12] Resources included peer-reviewed literature on use of cBHT (e.g., IJPC, 2018), cBHT preparation adverse event reports (FDA, 2018a, 2020a), information provided by compounding practitioners (see Public Access Folder), recent biannual outsourcing facility preparation reports (FDA, 2019a), and online marketing information from compounding pharmacies.

addition, high progesterone doses (> 200 mg) are also available in cBHT preparations, but have never been tested for safety or efficacy in FDA-approved products, thus raising a different set of safety concerns.

In summary, compared to compounded formulations, there are fewer FDA-approved dosage forms and strengths, and in many cases there is no comparable FDA-approved product. Therefore, even with the limited data available to the committee, it can be assumed that there are likely tens of thousands of different cBHT preparations (dosage forms and doses) available for patient use. This includes the wide array of different dosage forms, single active ingredient preparations, multiple active ingredient preparations, and an extensive range of different active ingredient doses and dose combinations.

Multihormone cBHT Preparations

Part of the appeal of compounding bioidentical hormones is that multiple hormones can be combined into a single dosage form that does not exist in a single FDA-approved product. In fact, of the 741 formulations identified by the committee, 289 were formulations containing more than one active pharmaceutical ingredient (API). While it may be convenient for patients to have multiple hormones combined into a single formulation, thereby reducing their medication burden, it remains unclear whether the combinations of these hormones are necessary or sufficient to elicit the desired effects, allowing the potential for patients to be exposed to undue risk without deriving any additional benefit. Moreover, the practice of combining multiple APIs in a single formulation is a complex process requiring careful consideration of drug–drug interactions as well as the compatibility of all the active and inactive ingredients in the dosage form (Pourkavoos, 2012).

In contrast to the wide variety of available multihormone cBHT preparations, there is only one FDA-approved fixed-dose combination bioidentical hormone product, Bijuva (TherapeuticsMD, 2018). The limited FDA-approved option is likely a result of the narrow conditions under which FDA approves products with two or more active ingredients. Unlike cBHT preparations, which may combine any number of hormones without first demonstrating safety or effectiveness, FDA-approved products that combine multiple drugs must not only provide evidence of safety and efficacy, but they must also demonstrate the combination improves the safety over any of the individual drug components alone (see Box 5-2).[13]

In addition, within the New Drug Application or Abbreviated New Drug Application submitted for all FDA-approved products is a description

[13] Fixed-combination prescription drugs for humans. 21 CFR § 300.50 (January 5, 1999).

BOX 5-2
FDA Policy and Guidance on Products Combining Multiple Drugs

FDA policy on fixed-dose combination drug products states that "two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective." FDA enumerates two special cases of this rule, which are when a component is added "to enhance the safety or effectiveness of the principal active component" and "to minimize the potential for abuse of the principal active component."[a,b] For drug manufacturers, this means they must provide clinical trial data on safety and efficacy, as for single active ingredient drugs, as well as data demonstrating that the inclusion of each active component of the drug is necessary for an increased efficacy or safety, or decreased potential for abuse.

While FDA does not offer guidance on the development of fixed-dose combination drug products, aspects of the agency's guidance on other combined products may offer insight into FDA's thinking on combination drug products. FDA recommends that product developers consider and evaluate the potential for interactions between components of the combination product. Other considerations include whether changes in the design or formulation may affect the safety and/or efficacy of the constituents or combined product as a whole and whether there is a strong biological rationale to justify the combination. FDA also recommends that several studies be performed, including human pharmacokinetic studies, dose ranging studies in humans, acute and repeat dose toxicity studies, and other potential safety monitoring based on the products' constituents (FDA, 2006, 2013).

[a] Fixed-combination prescription drugs for humans. 21 CFR § 300.50 (January 5, 1999).

[b] See Fixed-Combination and Co-Packaged Drugs: Applications for Approval and Combinations of Active Ingredients Under Consideration for Inclusion in an Over-the-Counter Monograph. *Federal Register* 2015-32246 (December 23, 2015). In 2015, FDA proposed new regulations for fixed-combination drugs that would continue to require fixed-combination drugs to meet one of these two special cases. At the time of this report, the proposed regulations had not been finalized.

of the manufacturing and quality processes involved,[14] including the "Chemistry, Manufacturing, and Controls" (CMC) section.[15] The CMC section is an extremely detailed set of documents with far more information than

[14] New drug application (NDA) and abbreviated new drug application (ANDA) are the mechanisms through which a drug manufacturer presents evidence to request that FDA approve their drug product. More information on this process can be found in Chapter 3.

[15] Content and format of an NDA. 21 CFR § 314.50 (February 22, 1985).

in an MFR. For example, the CMC section will include active and inactive ingredient potency reverification, container labeling, stability testing, and detailed manufacturing processes to control for quality attributes (Sheinin and Williams, 2002). FDA encourages that the CMC manufacturing process be further refined via the quality-by-design process through which quality is built into the drug product by identifying and controlling critical process parameters and attributes of the APIs, excipients, and final drug product. In drug manufacturing, this usually involves extensive drug product testing across batches, as well as strict control of process parameters as well as API and excipient attributes to minimize product variability (Yu et al., 2014). This is a more intensive process than what can be captured by a 503A compounding pharmacy or 503B outsourcing facility, but it provides a necessary comparative context.

cBHT ACTIVE INGREDIENTS

To prepare a cBHT formulation, the compounder must either purchase the pure active ingredient from a wholesaler or obtain the active ingredient from a suitable FDA-approved product, should one exist.[16] The pure ingredient is referred to as the API or bulk drug substance. FDA-approved products are required to use APIs that have been well characterized within an application for approval or in a Drug Master File (DMF), sections of which are not available outside of FDA because they contain proprietary manufacturing information.[17] As a result, the API pedigree, stability, potency, impurity profile, and other key characteristics are known and can be referenced by the drug manufacturer and FDA. This level of information far exceeds what information is routinely available to compounders when purchasing APIs because of the proprietary information contained in the DMF.

Excluding DHEA and pregnenolone, 8 of the 10 active ingredients reviewed by this committee are described in USP-National Formulary (NF) monographs for bulk drug substances (USP, 2019a). Federal law requires that APIs meet the standards of USP-NF if a monograph for that API exists.[18] The existence of USP-NF monographs for estriol and estrone, which are not components of FDA-approved products, allows them to be compounded.

[16] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

[17] DMFs are submissions to FDA used to provide confidential, detailed information about facilities, processes, and articles used in the manufacturing, processing, packaging, and storing of APIs (FDA, 2019b).

[18] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

Complex Characteristics of Active Ingredients Used in cBHT Preparations

The challenges of formulating the 10 APIs covered in this report represent a complex topic that has been described in great detail over many decades (Goodman Gilman et al., 1990), and the breadth of those challenges is beyond the purview of this report. However, this topic provides useful context for the committee to consider in their examination of the clinical utility of cBHT preparations.

In all formulation processes, it is important to consider the "formulatability" of APIs, meaning how easily the API can be made into a stable dosage form capable of consistently delivering it to the sites of action in the body. As a class, steroid hormones are recognized as presenting formulation difficulties, in part because of their poor water solubility (Benet et al., 2011), potential to be metabolized in vivo (Miller and Auchus, 2011), active uptake by cellular transporters (Hammes et al., 2005), and potential variablility (FDA, 2012; see Table 5-4).

To provide a closer look at the complexity of formulating APIs, the following sections discuss six API characteristics that must be considered during formulation to more reliably deliver hormones to the active site: particle size, polymorphism, solubility, purity, in vivo metabolism, and formulation stability. A related concept, formulation release rate, will also be discussed.

TABLE 5-4 Contributing Factors and Absorption Classifications of Bioidentical Hormones

Active	Water Solubility (mg/mL)	BDDCS	USP Monograph
Dehydroepiandrosterone	0.0635	NR	No
Estradiol	0.0036	1	Yes
Estradiol cypionate	NA	NA	Yes
Estriol	0.02734	NR	Yes
Estrone	0.03	NR	Yes
Pregnenolone	0.00706	NR	No
Progesterone	0.00881	2	Yes
Testosterone	0.0234	2	Yes
Testosterone cypionate	NA	NA	Yes
Testosterone propionate	NA	NA	Yes

NOTE: BDDCS = Biopharmaceutics Drug Disposition Classification System; Class 1 = high solubility; high permeability; rapid dissolution; Class 2 = low solubility; high permeability; NA = used in only injection products; NR = not reported.

SOURCES: Committee generated, using data from Benet et al., 2011, and NLM, 2020b.

Particle Size

API particle size and distribution strongly influence absorption, with small particles dissolving faster and more easily than large particles. Indeed, it is well recognized that hormone absorption by the body is associated highly with API particle size (Dahan et al., 2009). For example, many compounders acknowledge the importance of using "micronized" progesterone powder in cBHT preparations, but not all micronized progesterone powders are equivalent when it comes to particle size. The distribution and average of particle sizes among batches or lots of micronized progesterone API must be similar before they can be regarded as possibly equivalent (Yu et al., 2014).

Polymorphisms

Some powder hormone APIs are polymorphic, meaning they can form more than one solid crystal structure, and each crystal structure will have its own solubility characteristics (Sarkar et al., 2014; Stevenson et al., 2019), which thereby affect absorption (Censi and Di Martino, 2015).

Solubility

The low water solubility of reproductive hormones controls absorption from all routes of administration (oral, topical, injection/implant) and is compensated for many ways. For oral formulations, large daily doses are administered (Boyd et al., 2019), while with the topical route, lower doses are applied with the possible inclusion of penetration enhancers (Ng, 2018; Prausnitz and Langer, 2008) to compensate for poor aqueous solubility.

Purity

API purity can affect the efficacy of the drug (Roy, 2002). Absorption is a concentration-dependent process, so as the amount of active ingredient in an API is reduced, so will the amount absorbed into the body. Of note, 503A compounding pharmacies are not required to assess the purity of their APIs and are permitted to rely solely on the product certificate of analysis and expiry date as provided by the API manufacturer. If, at the 503A compounding pharmacy, an API becomes contaminated accidentally or degrades faster than expected because it was stored at the wrong temperature, the 503A compounding pharmacy may not detect those changes. In contrast, 503B outsourcing facilities and FDA-approved drug manufacturers

are required to perform confirmatory API purity testing before using APIs in compounding.[19]

In Vivo Metabolism

Hormones are targets of extensive in vivo cellular metabolism (Miller and Auchus, 2011) and transport (Siiteri et al., 1982), making it difficult for them to reach their sites of action reliably once absorbed. The liver, for example, effectively metabolizes hormones that are delivered orally, another reason why oral doses are so much higher than topically delivered doses (von Schoultz, 2009). In addition, for any given route of administration (oral, topical, injected/implanted) there is significant variability between patients in the resulting blood levels of hormones and their metabolites (Kuhl, 2005), and there is even significant day-to-day variability within the same patient (Brambilla et al., 2007; Kraemer et al., 2003). For further discussion on bioavailability of cBHT preparations, see Chapter 6.

Formulation Stability

FDA-approved drug manufacturers must test their products for API stability within the formulation and for their ability to safely release hormones over time.[20] Demonstrating API stability in a formulation is of obvious importance. For example, if a dissolved API crystalizes out of solution in a topical cream, it may decrease the bioavailability of the hormone, decreasing the effectiveness of the cream (Garnero et al., 2018). This scenario can happen simply because the cream loses water over time if it was not in a well-sealed package. As a second example, for many formulations, the order of ingredient mixing, inclusion of solubilizers, and other process variables are critical for formulation stability. This is especially the case for topical preparations, as microstructures are formed between ingredients within the dosage form (Jeong et al., 2003). Simple two or three ingredient topical formulations or use of a single premixed commercial base may not be adequate to produce a formulation with suitable stability. For comparison, Box 5-4 lists the 10 inactive ingredients incorporated into Estrace Cream, which are all required for prolonged product stability.

In contrast, 503A compounding pharmacies are not required to demonstrate that APIs are stable in formulations for the life (i.e., expiry date or beyond use date) of their products. Neither are compounders required to measure hormone release rates from cBHT preparations. For example,

[19] Testing and approval or rejection of components, drug product containers, and closures. 21 CFR § 211.84 (September 8, 2008).

[20] Special testing requirements. 21 CFR § 211.167.

at a November 2019 open session meeting, Dr. Gary S. Donovitz (BioTE Medical, LLC) who uses a 503B outsourcing facility to prepare testosterone pellets for use in their practice was asked during an open session meeting whether their group tested the pellets to determine the rate of testosterone release over time. Dr. Donovitz expressed that his practice does not conduct such testing, but instead examines the peak serum testosterone levels in patients, using certain target ranges for optimization (NASEM, 2019c).

All of the factors reviewed in this section must be taken into account when developing drug formulations with hormone APIs. Formulations require rigorous testing and improvement over time, before knowing that they can reliably, over time, deliver hormones through the skin, gastrointestinal tract, and tissues. However, the materials, methods, and quality standards followed differ among pharmacies when preparing cBHT preparations, even when filling identical prescriptions.

Examples of Complexity: Formulations, Dosage Forms, and Potency

As a formulation's complexity increases, so does the potential for product failure. For example, Bi-est (formulated with estradiol and estriol, in varying amounts) and Tri-est (formulated with estradiol, estriol, and estrone, in varying amounts) are commonly prescribed cBHT formulations.[21] An even more complex formulation is "Arousal Cream," which contains six active ingredients. Unless formal stability studies on these complex formulations are conducted and disclosed, there is cause for concern regarding the stability and bioavailability of every multi-ingredient compounded preparation.

The level of potency is also an important consideration. For compounded preparations, USP has established a ±10 percent potency deviation range for most compounded preparations (USP Compounding Expert Committee, 2014). Yet, differences in the potency of cBHT preparations have been documented between compounding pharmacies. For example, when compared with product labeling, estradiol capsule potency varied from –26 percent to +5 percent, estradiol cream potency varied from –11 percent to +1.4 percent, progesterone capsule potency varied from –9 percent to +31 percent, and progesterone cream potency varied from –5 percent to +12 percent of the label (Stanczyk et al., 2019). For reference, FDA-approved products typically must maintain potency within a ±10 percent range from the label (Blessy, 2014) to maintain safety and effectiveness (FDA, 2004).

[21] As discussed in Chapters 2 and 8, it is difficult to secure quantitative data on the prescription rates and dispensing practices for specific cBHT formulations, doses, and dosage forms; however, available data suggest that Bi-est and Tri-est, available in varying amounts and dosage forms, are commonly compounded preparations (IJPC, 2018; NABP, 2019).

Illustrative Example of Complex cBHT Preparations: Hormone Pellets

Hormone pellet therapies are complex formulations that must be prepared to exacting specifications in order to safely, reliably, and repeatedly deliver a uniform amount of hormone over time. Pellets are implanted subcutaneously and are expected to release hormone(s) at a controlled uniform rate, typically over weeks to months (McCullough, 2014). As such, they are controlled release dosage forms, which makes them different from the more routinely compounded "immediate release" therapies such as topical creams, oral capsules, or immediate release injections.

The committee found multiple examples of cBHT pellets for estradiol, testosterone, and progesterone, available in varied strengths (see Appendix F).[22] In regard to the scope of available pellet therapies, the testosterone replacement market alone has been described as a multibillion dollar industry (McCullough, 2014).

Several factors affect the ability of a pellet to reliably release hormone(s) over time, including content uniformity and pellet size and shape (length, width, surface area). Content uniformity is how well the hormone(s) and inactive ingredients are mixed together. As pellets slowly dissolve over time, and thereby slowly release hormone(s) over time, any pockets of hormone crystals (e.g., from a nonuniform mixture) within the pellet may deliver an unintended bolus of hormone(s) to the body.

For most pellets, the size, shape, and surface area of the pellet must be uniform among all pellets of the same dose, and the pellet surface area must be proportional between different dose pellets. That is because the dose delivered is proportional to the surface area of the pellet (McCullough, 2014). Whether compounded or FDA approved, testosterone pellets for men are usually implanted in sets of 10 or more (Glaser and York, 2019; McMahon et al., 2017), and each is expected to deliver hormone(s) at the same rate (McCullough, 2014). Small deviations in length or width will change the rate of hormone delivery. Note that pellets are much smaller than the products a pharmacist typically prepares. For example, a Testopel pellet is 3 mm wide and 8 mm long (McCullough, 2014), which is about the size of a single grain of rice. To dispense a pellet in response to a patient prescription, a pharmacist would have to own and know how to operate special equipment that can mix, dry, extrude, package, and sterilize the pellets. Such equipment is simply not found in the majority of pharmacies. It also cannot be made "on demand." Also, to be sure the pellets are of

[22] Resources included peer-reviewed literature on the use of cBHT (e.g., IJPC, 2018), cBHT preparation adverse event reports (FDA, 2018a, 2020a), information provided by compounding practitioners (see Public Access Folder), recent biannual outsourcing facility preparation reports (FDA, 2019a), and online marketing information from compounding pharmacies.

uniform size, the pharmacist would have to be able to measure small differences in length and width, on the scale of ≤ 0.3 mm, among same dose pellets.

To prepare pellets simply requires special compounding equipment that is only found in pharmaceutical manufacturing facilities. Also to test a batch of pellets to show they are the correct size, shape, have proper content uniformity, and deliver hormones at a uniform prespecified rate, requires both complex physicochemical testing (specialized dissolution testing) and analytical test methods. Again, such testing is only available in specialized pharmaceutical analytical testing facilities.

Because hormone pellets deliver hormones slowly over an extended period of time, including up to 2 to 5 months (Glaser and York, 2019; McCullough, 2014), specialized bioavailability study designs are required to show how reliable and consistent the delivery happens in humans. That is, pellets require the types of bioavailability study designs applied to depot injection products, which deliver active ingredients over weeks and months. As will be discussed in Chapter 6, compounded preparations are not required to be tested for bioavailability. Also the standard in vitro batch release tests do not capture information required to have assurance that a hormone pellet can safely and uniformly deliver hormones over long time periods. This may explain why there is evidence of significant adverse reactions, indicative of hormone overdose, in groups of patients that have received hormone pellet therapy (Jiang, 2019).[23] For example, a higher incidence of mood swings, breast tenderness, hair pattern changes, acne, weight gain, and dyslipidemias were reported in woman that received compounded pellets containing estradiol or testosterone, when compared with woman receiving an FDA-approved hormone product. Also in the same study, woman receiving pellet products had significantly higher and more variable serum concentrations of estradiol and testosterone, when compared with woman receiving an FDA-approved product (Jiang, 2019). There is also evidence of compounding pharmacies substituting inactive ingredients into pellet products (e.g., a cholesterol base for a steric acid base), which would completely change the release characteristics of the pellet,[24] a formulation change that could clearly put patients at risk.

Difficult to Compound

Given the complexity of the compounding process as discussed above, the Federal Food, Drug, and Cosmetic Act (FDCA) asks FDA to develop

[23] *State of Tennessee v. HRC Medical Centers Inc.* 2012. Robert E. Cooper, Jr. (Circuit Court for Davidson County, TN).

[24] Accusation in *Herold v. University Rx Specialist*, Case No. 4347 (2015).

BOX 5-3
Difficult to Compound List

In 2016, an internal FDA working group proposed six criteria to evaluate whether drug products or categories of drug products should be included on the list. After review by FDA's Pharmacy Compounding Advisory Committee, the following criteria were published in a July 28, 2017, *Federal Register* notice:

1. The complexity of the formulation;
2. The complexity of the drug delivery mechanism;
3. The complexity of the dosage form;
4. The complexity of the bioavailability issues;
5. The complexity of the compounding process; and
6. The physicochemical or analytical testing complexity.

FDA has stated that it will consider these criteria individually and collectively when evaluating whether a drug product or category of drug products is demonstrably difficult to compound.*

* Drug Products That Present Demonstrable Difficulties for Compounding Under the Federal Food, Drug, and Cosmetic Act; Establishment of a Public Docket. 82 FR 35214 (July 28, 2017).

regulations identifying drugs and drug categories that "present demonstrable difficulties for compounding" and to establish a Difficult to Compound List, which would preclude the use of listed drugs in compounded preparations.[25] When considering whether or not a drug is difficult to formulate, both the active ingredient and the dosage form should be considered. Relevant to this report, most of the cBHT APIs and certain cBHT formulations exhibit one or more of the complexities discussed in the criteria for the Difficult to Compound List (see Box 5-3).

[25] See Drug Products That Present Demonstrable Difficulties for Compounding Under the Federal Food, Drug, and Cosmetic Act; Establishment of a Public Docket. 82 FR 35214 (July 28, 2017) (FDA announces development of criteria to evaluate drugs as demonstrably difficult to compound under 503A and 503B).

Conclusion 5-2

Compounded bioidentical hormone therapy (cBHT) pellet formulations may be difficult to compound given the complexity of drug delivery mechanism, lack of required bioavailability testing, insufficient guidance for compounders, and the need for specialized equipment. Given the broad scope of available cBHT pellet formations marketed for use, and questions regarding difficulty in compounding, there are concerns for safety and effectiveness.

INACTIVE INGREDIENTS

All FDA-approved products and those compounded by 503B outsourcing facilities are required to list their inactive ingredients on their container labeling according to the FDCA's provisions regarding misbranded drugs.[26] While there is no explicit requirement in Section 503A to include inactive ingredients on the label, the FDCA section on misbranded drugs that applies to all drugs (manufactured or compounded) includes a requirement that drugs list inactive ingredients on the container label.[27,28] However, 503A pharmacies and other health care facilities may not have the infrastructure to provide appropriate information on inactive ingredients, and as a result, inactive ingredients labeling may not be routinely followed for compounded drugs (ISMP, 2018). Therefore, it may not be possible for many patients to know what inactive ingredients were used in the formulation of a given cBHT preparation. If a patient were to have an allergic reaction to a compounded preparation, it may be difficult to review the inactive ingredients contained therein when considering what the patient may have reacted to. This seems unbalanced, especially as a primary rationale for compounding is to provide products for patients that may have allergies to FDA-approved products (McBane et al., 2019). In contrast, compounded preparations made at 503B outsourcing facilities are required to list inactive ingredients directly on the label, and given FDA's increased oversight role

[26] See Section 503B(a)(10) of the Federal Food, Drug, and Cosmetic Act.

[27] Requirements on content and format of labeling for human prescription drug and biological products. 21 CFR § 201.56 (December 4, 2014).

[28] Federal Food, Drug, and Cosmetic Act. 21 U.S. Code Chapter 9.

BOX 5-4
Inactive Ingredients in Estrace Cream, an FDA-Approved Product

For all FDA-approved products, the inactive ingredients are listed on the drug container. The ingredients must be sourced from FDA-licensed establishments. An example of the variety and number of inactive ingredients commonly included in FDA-approved products is provided in Table 5-5 for Estrace Cream.

SOURCES: Committee generated, using information derived from Chang et al., 2013; Garg et al., 2015; Rowe et al., 2006; Warner Chilcott, 2005.

TABLE 5-5 Inactive Ingredients in Estrace Cream and Their Function

Ingredient	Purpose
Water	Solvent
Propylene glycol	Humectant; preservative; solvent or cosolvent
Stearyl alcohol	Stiffening agent; emollient; weak emulsifying agent
White ceresin wax	Stiffening agent
Mono and diglycerides	Emulsifier; stabilizer; emollient; plasticizer
Hypromellose	Gelling agent
Sodium lauryl sulfate	Emulsifier; solubilizer
Methylparaben	Preservative
Edetate disodium	Chelating agent; preservative
Tertiary-butylhydroquinone	Antioxidant

of 503B facilities, the agency would likely detect noncompliance with this requirement (see Box 5-4).[29]

Some compounding suppliers offer premixed commercial bases (solutions, creams, semisolids) to which active ingredients can be added to prepare compounded formulations. A few examples include VersaBase Cream, VersaBase Gel, Lipoderm, and MucoLox (Clark and Hover, 2016). These make compounding easier by reducing the number of ingredients and steps needed to prepare a compounded product. In some cases, base suppliers offer some documentation to aid in preparing the MFR, along with limited data implying that the base delivers the hormone through

[29] See Section 503B(a)(10) of the Federal Food, Drug, and Cosmetic Act.

the skin or mucous membranes. As an example, instructions for preparing progesterone in Versabase Cream are available online (Allen, 2017). The product contains only three ingredients: micronized progesterone, pentylene glycol, and Versabase Cream. Many of these base mixtures, however, are not specialized for specific formulations (Medisca, n.d.) as are FDA-approved products, and they are not required to be tested for their ability to deliver hormones through the skin or mucous membranes with the same rigor as FDA-approved products.

Some cBHT preparations are described in USP monographs. However, the inactive ingredients are not always precisely defined within those USP monographs, and the compounder is permitted to apply their skill and art when selecting inactive ingredients. For example, Estradiol Vaginal Cream USP describes the cream component as, "a stable cream base." Similarly, Estradiol Cypionate Injection USP instructs the compounder to use "a suitable oil" as the injection vehicle (USP, 2019b).

For compounded USP monograph preparations, this lack of specificity around inactive ingredients may lead to different cream base products being used by different compounders. In these cases, an estradiol cream preparation purchased from one compounding pharmacy may have different inactive ingredients then a product with the same name purchased from a second compounding pharmacy. Differences in inactive ingredients can affect the availability and absorption of cBHT active ingredients, given their low solubility and high metabolism (Panakanti and Narang, 2012), which would result in patients being exposed to differing amounts of the active ingredient.

Similarly for preparations without USP monographs, such as cBHT pellets, the inactive ingredients used may vary between compounders. For example a 25 mg estradiol pellet from one compounder may contain different ingredients than an estradiol pellet provided by a second compounder. There is a reported case where the same pharmacy used a different base to compound testosterone pellets, without knowing the effect of the formulation change on stability.[30]

[30] Accusation in *Herold v. University Rx Specialist*, Case No. 4347 (2015).

Conclusion 5-3

In contrast to FDA-approved drug products, compounded bioidentical hormone therapy (cBHT) preparations lack standardized production methods, potentially leading to state-by-state and even pharmacy-by-pharmacy variability in the medications dispensed to patients. In addition, cBHT active dose ranges are wider, both lower and higher than corresponding bioidentical FDA-approved drug products, and inactive ingredients (e.g., excipients) can be difficult to identify, creating concerns about cBHT safety and efficacy.

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6

Bioavailability of Compounded Bioidentical Hormone Preparations

There is little published information on the bioavailability and pharmacokinetics of compounded bioidentical hormone therapy (cBHT) preparations.[1,2] The lack of data results largely from the fact that compounding pharmacies making cBHT preparations are not required to conduct clinical studies to determine the bioavailability of a finished preparation (FDA, 2016, 2017). Moreover, the sheer diversity and heterogeneity of cBHT preparations and pharmacy practices makes any comparative bioavailability studies difficult to conduct.[3] While it is true that compounding provides alternate methods of drug delivery to fit patients' unique health needs (U.S. Senate, Special Committee on Aging, 2007), it is also important that when a cBHT preparation is delivered using a route of administration that differs from that of a U.S. Food and Drug Administration (FDA)-approved product with the same active pharmaceutical ingredient (API) ingredient—often the case with compounded preparations—its bioavailability, and ultimately its safety and efficacy, would be unknown.

In the absence of bioavailability data, there are important variables to consider, including, but not limited to, the particle size of the API, degree of mixing and type of mixing equipment used to make a given preparation, route of drug administration, and presence of other excipients (nonactive

[1] Bioavailability refers to the amount of administered drug or substance within the body that is free to have an active effect on biological targets.

[2] Pharmacokinetics is the study of the kinetics of drug absorption, distribution, metabolism, and elimination.

[3] See Chapter 5 for a review of the various cBHT preparations.

ingredients in the preparation). These variables can each decrease or increase bioavailability of the API (Allen and Ansel, 2013; Khadka et al., 2014; Kuhl, 2005; Remington and Beringer, 2006).[4] For example, while the APIs used in two cBHT preparations prepared at two different compounding pharmacies may be identical, the excipients in the two preparations can have differing physicochemical properties that can potentially affect the bioavailability of APIs in the two compounded preparations dispensed to patients (Allen and Ansel, 2013; Khadka et al., 2014; Remington and Beringer, 2006).

Conceivably, the results of one-off studies would not be that useful given the potentially small number of individuals who would receive any of the large number of different cBHT preparations. However, in the absence of bioavailability data, the specific effect of these variables on the safety and efficacy of the cBHT preparations is unknown. While the committee appreciates the potential of personalized medicine and what it can offer to patients, the balance of safety and effectiveness with personalized medicine is a balance that needs to be further explored.

Conclusion 6-1

The immense number of potential combinations of different hormones, excipients, dosage forms and strengths, as well as the lack of uniformity of compounded bioidentical hormone therapy (cBHT) preparations, make determining definitive bioavailability of those preparations difficult. Without reliable bioavailability data, an accurate characterization of the safety and effectiveness of cBHT preparations is not possible.

MEASURING CONCENTRATIONS OF STEROID HORMONES

Current clinical guidance suggests there is insufficient evidence to support claims that multiple blood, serum, or saliva tests can be used to precisely individualize hormone therapy (e.g., ACOG, 2018; Endocrine

[4] This report does not specifically address the role of protein binding and its effect on bioavailability of compounded preparations owing to lack of data. Also, the potential effect of body mass index (BMI) affecting steroidal hormone levels in postmenopausal women receiving compounded preparation is not addressed owing to lack of data.

Society, 2019; NAMS, 2020; Santoro et al., 2016).[5] Because no studies have demonstrated that using hormone concentrations to guide treatment is effective or useful, the American College of Obstetricians and Gynecologists recommends using clinical symptoms to guide treatment (ACOG, 2018). Nonetheless, some prescribers of cBHT use hormone imbalance as a rationale and guide for treating the symptoms of menopause (NASEM, 2019a,b).[6]

Characterizing hormone imbalance typically involves measuring hormone concentration levels in saliva, plasma, serum, or urine, and patients interested in this approach can find websites offering hormone balance test kits. Patients collect samples of saliva and/or blood and mail them to a designated laboratory. These labs often use bioanalytical methodology that lacks the rigors of the validated bioanalytical methods required to analyze pharmacokinetic samples collected in FDA-approved clinical studies (Herold and Fitzgerald, 2003; Kane et al., 2007). In addition, differences in steroid hormone levels can depend on the matrix used to measure the hormone concentration. One study, for example, examined the distribution of progesterone in venous whole blood, venous serum, fingertip capillary blood, and saliva after topical application of either cream or gel formulations compounded at a local pharmacy (Du et al., 2013). After topical administration of progesterone, saliva and capillary blood levels were 10-fold and 100-fold greater, respectively, than those seen in serum or whole blood. The investigators who conducted this study concluded that relying on serum levels of progesterone for monitoring topical administration of progesterone could lead to underestimation of tissue levels and consequent overdose.

Furthermore, in 2007, the Centers for Disease Control and Prevention (CDC) launched a project focused on standardizing hormone measurement (Vesper et al., 2008). In the project communication materials, CDC states

> Despite physician's wide spread use of hormone test results, the laboratory measurement of steroid hormones is subject to extreme variability especially when hormones are present in low concentrations, as is usually the case for testosterone in women and children, and for estradiol in men, children, and postmenopausal women. (CDC, 2008)

[5] As an example, the North American Menopause Society states that hormone concentrations are not required to determine whether a woman has the "right amount" of hormones, since the optimal hormone concentrations in postmenopausal women have not, in fact, been established (NAMS, 2020).

[6] More information is available at https://www.ucihealth.org/blog/2019/03/bioidentical-hormone-therapy (accessed October 23, 2019).

Measuring Hormone Concentrations: Salivary Testing

Salivary testing is often promoted by online analytical laboratories as a convenient, noninvasive method for hormone sampling. At the same time, several professional medical societies have issued public statements that saliva testing is unnecessary and has not been proven to be accurate or reliable, mainly because the variation in the day-to-day or within-a-day hormone concentrations in an individual is large enough to make any one measurement uninformative (ACOG, 2018; Endocrine Society, 2019; Goodman et al., 2011; NAMS, 2017). In one study, for example, researchers compared salivary versus serum testosterone concentrations in postmenopausal women receiving transdermal testosterone supplementation (Flyckt et al., 2009). The data suggested there was no correlation between salivary testosterone and any of the serum testosterone measurements (see Figure 6-1), leading the researchers to conclude that the results

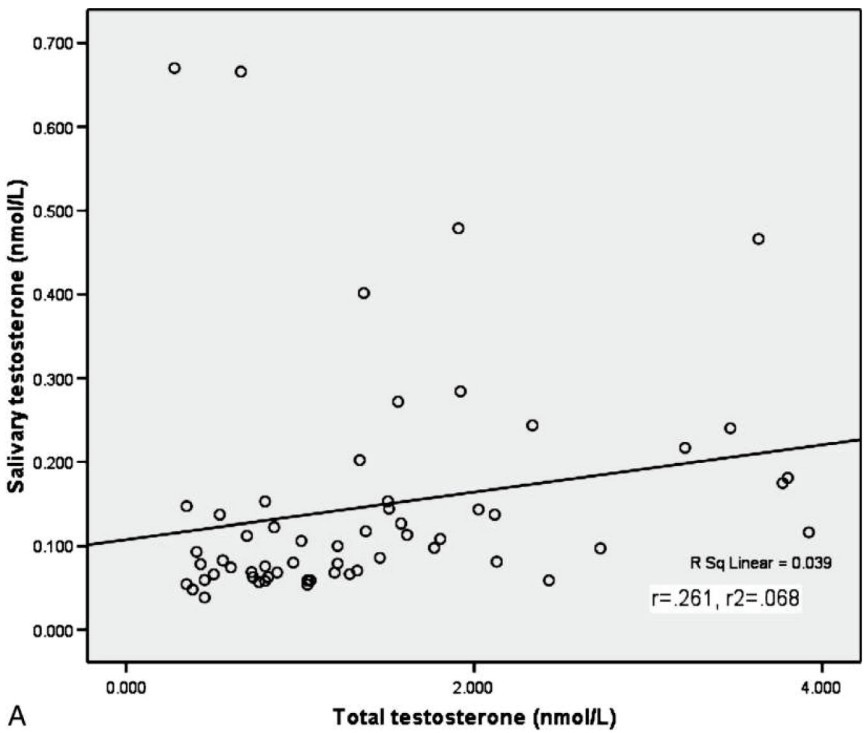

FIGURE 6-1 Correlation between salivary testosterone (T) and serum free (T) (nmol/L).
SOURCE: Flyckt et al., 2009.

did not support the routine use of salivary testosterone concentrations in postmenopausal women.

While the bioanalytical method used in the comparative analysis in Figure 6-1 is a validated radioimmunoassay (Flyckt et al., 2009),[7] there have been specific concerns over the accuracy and reliability of immunoassays to assess testosterone measurements (Cao et al., 2007; Davis et al., 2019). A recent consensus position statement from several medical associations on the use of testosterone therapy in women stated that direct assays for the measurement of total and free testosterone are highly unreliable (Davis et al., 2019). Concerns regarding immunoassay assessments of steroid hormones are the result, in part, of a lack of immunospecificity caused by cross-reactivity with other steroids having a similar structure; poorly optimized quantification; and improper validation against standards (Clifton et al., 2016; Holst et al., 2004; Keevil et al., 2014). Recently, several authors have demonstrated that liquid chromatography/tandem mass spectrometry (LC-MS/MS) methodology can reliably and accurately measure testosterone levels in both male and female saliva samples (Clifton et al., 2016; Keevil et al., 2014), highlighting potential benefits in its use in cBHT research. (See section on Bioanalytical Methods below for an additional discussion on this topic.)

Measuring Hormone Concentrations: Urine Testing

Physicians who prescribe cBHT may also advocate for the use of urine testing to measure hormone levels. At the committee's open session in May 2019, invited speakers Lyn Hogrefe, M.S., and David Rosensweet, M.D., noted that they prefer urine hormone testing because it is easier for patients and less expensive than other forms of testing (NASEM, 2019a,b). Advocates for this approach also claim that urine testing allows them to evaluate safety through measuring hormone metabolites, and that urine sampling provides a measure of free, "bioavailable" hormones. Importantly, while hormone level testing at clinical labs, for the purpose of checking normal values, may serve a clinical purpose, this type of testing stands as a distinct issue from that of testing for the bioavailability of a compounded preparation, which is lacking.

[7] Reports that include serum concentrations of steroid hormone in cBHT preparations often use radioimmunoassays/immunochemiluminometric assay methods to measure steroid hormone concentrations (Glaser et al., 2013; Miller et al., 2000; Wren et al., 2003b).

Measuring Hormone Concentrations: FDA Requirements for FDA-Approved Hormone Products

As a comparison to the various protocols described above, FDA requires the measurement of steroid hormones in plasma or serum in bioequivalence studies with pharmacokinetic endpoints (FDA, 2019a). For example, FDA guidance on measuring estradiol in bioequivalence studies of estradiol vaginal tablets, gels, or creams identifies "estradiol in plasma" as the appropriate biological fluid to measure estradiol (FDA, 2011a, 2014, 2019a). Similar FDA guidance specifies plasma or serum as the appropriate biological fluid for measuring the levels of other steroid hormones, such as progesterone and testosterone, in clinical studies with pharmacokinetic endpoints (FDA, 2011b, 2019b).

Conclusion 6-2

There is no established evidence base to support the routine clinical use of steroid sex hormone levels for guiding the dosing in the treatment of menopausal symptoms.

BIOANALYTICAL METHODS TO MEASURE THE BIOAVAILABILITY OF STEROID HORMONES

LC-MS/MS is the gold standard methodology used today to support clinical studies with pharmacokinetic endpoints (FDA, 2018). LC-MS/MS is typically used because of the selectivity and specificity of the detection methodology, a requirement of validated bioanalytical methods. Examples of commercially available validated LC-MS/MS bioanalytical assays exist for many of the bioidentical hormones on the market today (see Table 6-1).

Recently, investigators evaluated urinary estrogen and progesterone metabolites using dried filter paper samples and gas chromatography with tandem mass spectrometry (Newman et al., 2019). This prospective observational study compared the results of urine and serum analyses. A secondary aim of the study compared results from dried urine samples collected at four times over a 10- to 14-hour time period (the 4-spot method) and the 24-hour collection method, which collects liquid urine samples over a full 24-hour period. Researchers obtained similar results from the 4-spot dried urine and the 24-hour liquid urine collection methods. Furthermore, based on the results of a comparison between dried urine and serum assays, the authors concluded that the dried urine assay may be a good surrogate for serum testing in clinical assessments of hormone disorders.

TABLE 6-1 Examples of the Bioanalytical Methods Used to Analyze Bioidentical Hormones in Blood/Serum/Plasma from Subjects Who Were Administered cBHT

Study	Analyte	Bioanalytical Method	Lower Limit of Quantitation
Sood et al., 2013	Estradiol	High-performance liquid chromatography (HPLC) tandem mass spectrometry	2.5 pg/mL
	Estrone	HPLC-tandem mass spectrometry	2.5 pg/mL
	Estriol	Competitive binding immunoenzymatic assay	0.07 ng/mL
	Progesterone	Competitive binding immunoenzymatic assay	0.08 ng/mL
Pickar et al., 2015	Unconjugated estradiol	HPLC-tandem mass spectrometry	25.3 pg/mL
	Unconjugated estrone	HPLC-tandem mass spectrometry	5 pg/mL
	Total estrone	HPLC-tandem mass spectrometry	0.1 ng/mL
	Progesterone	HPLC-tandem mass spectrometry	0.4 ng/mL
Singh et al., 2006	Total testosterone	HPLC-tandem mass spectrometry	0.5 ng/dL

SOURCES: Pickar et al., 2015; Singh et al., 2006; Sood et al., 2013.

BIOAVAILABILITY OF COMPOUNDED BIOIDENTICAL HORMONE THERAPY PREPARATIONS

From the limited bioavailability data on cBHT preparations that exist in the literature, the following four studies on compounded estrogen cream, testosterone pellets, progesterone cream, and a lozenge containing estradiol, progesterone, testosterone, and dehydroepiandrosterone (DHEA) serve as examples of how such studies are conducted.

Example Study 1: Compounded Estrogen Cream

Study Design and Results

One group of investigators (Sood et al., 2013) conducted a pharmacokinetic evaluation of cBHT preparations as part of a randomized, blinded, four-arm, 16-day clinical trial of 40 postmenopausal women. The study arms assigned women to receive a compounded cream containing a commonly used 80:20 ratio of estriol and estradiol (Bi-est) and 100 mg of compounded oral progesterone or a conventional estradiol patch (Vivelle-Dot 0.05 mg) and oral progesterone capsule (Prometrium 100 mg). The Bi-est creams were compounded to include a dosage of 2.0 mg (1.6 mg estriol/0.4 mg estradiol),

2.5 mg (2 mg estriol/0.5 mg estradiol), or 3.0 mg (2.4 mg estriol/0.6 mg estradiol).

The investigators measured serum concentrations of estradiol, estrone, estriol, and progesterone, and generated a 24-hour pharmacokinetic profile after the first and last application of the cream or patch. The resulting analysis showed that estradiol exposure at steady-state—as determined after the last application—for all strengths of the compounded cream was less than that from the patch, though hormone levels for test subjects who received 3.0 mg of the compounded Bi-est preparation were not statistically different from those who received the patch (see Figure 6-2). The American Medical Association commented on this study, concluding that given the unpredictable pharmacokinetics of compounded formulations, the use of cBHT cannot be supported in comparison to well-tested FDA-approved hormone therapy options (AMA, 2016).

Study Limitations

In this study, participants who received one of the compounded estrogen preparations using the Bi-est ratio had wide fluctuations in their estradiol concentrations both after the initial administration as well as at steady-state. In contrast, estradiol absorption with the patch was more consistent across subjects. Participants receiving one of the three compounded dosage formulations based on the Bi-est 80:20 ratio had lower estrone concentrations than those from the patch. There were certain limitations with

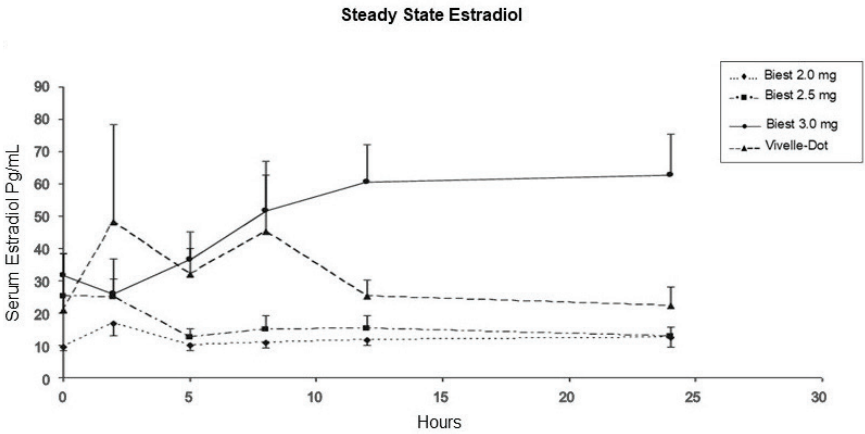

FIGURE 6-2 Steady-state serum estradiol concentration time course.
NOTE: Serum estradiol (pg/mL) as a function of time in hours (measured on days 15 and 16).
SOURCE: Sood et al., 2013.

the assay for measuring estriol, and as a result most subjects had estriol concentrations that were below the lower limit of detection. Progesterone concentrations were relatively similar after administration of the compounded and conventional bioidentical progesterone dosage forms in all four groups, suggesting that micronized progesterone is similarly absorbed across compounded and conventional dosage forms (Sood et al., 2013). However, the most informative bioavailability comparisons are those conducted between identical dosage forms, so a more appropriate reference in the study would have been an FDA-approved hormone product such as estradiol cream, estradiol gel, or estradiol spray products.

Another limitation of the study was the small number of subjects—between 7 and 10—in comparative arms of the study. Furthermore, given that Vanicream was used as the base for all three compounded estrogen formulations, the study results are not generalizable to all possible dosage formulations using the 80:20 Bi-est ratio. Variations in the content uniformity of estradiol and progesterone in compounded combined forms of oral capsule and transdermal cream preparations sourced from different compounding pharmacies is a concern among some professional medical associations (Davis et al., 2014; Stanczyk et al., 2019).

Regardless of the limitations of the study, the low and variable concentrations of serum estradiol obtained with the 2.0 and 2.5 mg Bi-est preparations in this study are concerning and cast doubts on the ability of compounded creams to provide relief of vasomotor symptoms and protect against bone loss. One case, for example, found that a patient treated for vasomotor symptoms with a dosage formulation using the Tri-est ratio (80 percent estriol, 10 percent estrone, and 10 percent estradiol) for several months experienced an initial relief of symptoms that returned even after increasing the dose (Davis et al., 2014). The patient's symptoms later improved after the prescribing physician switched the patient to an FDA-approved estradiol transdermal delivery system.

Example Study 2: Compounded Testosterone Subcutaneous Pellet

Study Design and Results

Investigators (Glaser et al., 2013) conducted a pharmacokinetic study in 12 previously untreated postmenopausal women who each received 100 mg testosterone as a subcutaneous implant compounded by a local pharmacy in Cincinnati, Ohio. The research team measured serum total testosterone at baseline, 4 weeks, and 16 weeks following the testosterone pellet implantation. Total testosterone was measured by an immunoassay (Bayer Advia Centaur), and for comparison a duplicate specimen was sent to a second lab for measurement by liquid chromatography. There were significant

interindividual variability in testosterone concentrations at week 4, mean serum level was 190.8 ± 80 ng/dL (range 83–368 ng/dL, CV 41.9 percent) (see Figure 6-3) and week 16 (CV 41.6 percent). These levels exceed the serum total testosterone reference range of 8–60 ng/dL in women (Mayo Clinic Laboratories, 2020).

The authors stated that the concept of using a single serum testosterone concentration measurement to guide therapy is inherently unreliable, extremely variable, and ignores the complexity of the physiologic events that controls hormone production and release. Instead, the authors concluded, safety, tolerability, and clinical response should guide therapy (Glaser et al., 2013).

Considerations Related to the Use of Compounded Testosterone

In contrast to the conclusions reached by Glaser et al. (2013), a 2019 global consensus position statement, endorsed by multiple professional medical societies, recommended against the use of compounded testosterone in women (Davis et al., 2019). The report states that "blood total testosterone level should not be used to diagnose hypoactive sexual desire disorder/dysfunction." The report recommended that treatment should be with formulations that achieve blood concentration of testosterone that approximate premenopausal physiological concentrations (Davis et al., 2019).

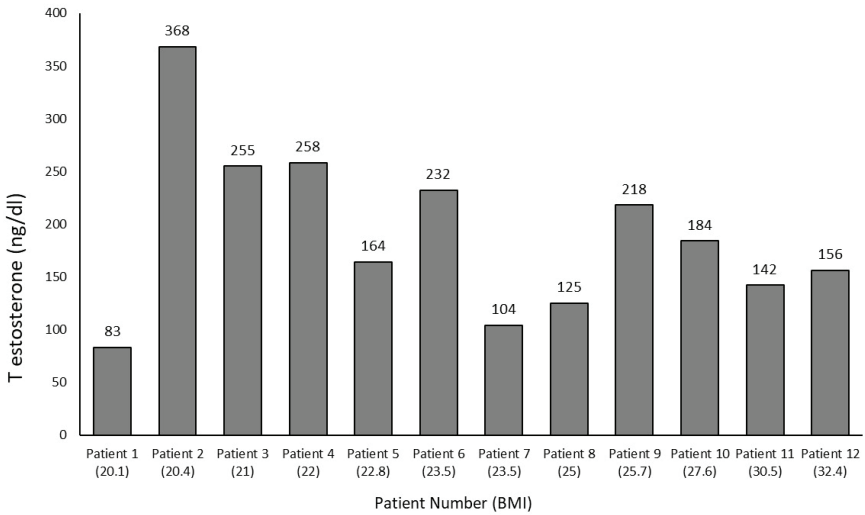

FIGURE 6-3 Serum testosterone concentrations in 12 female patients 4 weeks after therapy with a 100 mg testosterone implant.
SOURCE: Glaser et al., 2013.

The potential differences in the use of testosterone in therapeutic treatment plans for women versus men is another consideration regarding compounded testosterone. In women, measurement of serum total testosterone is used only to exclude high baseline or supraphysiological concentrations (Davis et al., 2019). In men with hypogonadism, however, measuring total testosterone during hormone therapy in conjunction with symptoms relief is part of the treatment plan (Bhasin et al., 2018).

Researchers have also expressed concerns regarding the quality control of compounded testosterone preparations, in terms of a lack of uniformity in testosterone content and its potential to compromise the safety and efficacy of treatment (Grober et al., 2015). One study tested 7 gel testosterone preparations and 3 cream testosterone preparations from 10 compounding pharmacies within the Toronto, Canada, area. Results showed significant variability both within and between pharmacies in terms of the measured concentrations of testosterone in the finished compounded preparations (Grober et al., 2015).

Finally, to serve as a potential reference point, transdermal testosterone cream is available as a traditionally manufactured product in Australia, 1 percent Androfeme (Lawley Pharmaceuticals, 2016), and has publically available bioavailability data to consider. The steady-state pharmacokinetics of Androfeme was investigated after daily application for 21 days in healthy postmenopausal women (Fooladi et al., 2015). Serum total testosterone, free testosterone, sex hormone binding globulin, and metabolic concentrations were measured using LC-MS/MS. On day 22, 5 mg testosterone cream restored both total and free testosterone levels to levels above and within the reference range, respectively, for premenopausal women.

Example Study 3: Compounded Progesterone Cream

Study Design and Results

A randomized, crossover clinical trial was conducted in 10 postmenopausal women to investigate the bioavailability of 80 mg of progesterone from compounded cream or gel applied daily to the inner thigh for 14 days (Du et al., 2013). Metered doses of compounded progesterone cream or gel were prepared by a compounding pharmacy, and on day 14 of the study, the investigators collected serial venous blood, fingertip capillary blood drawn just prior to drug application, and saliva samples up to 24 hours after the final application. The analysis was conducted using chromatographic purification followed by radioimmunoassay. Bioavailability data (see Table 6-2) showed that topical application of progesterone produced saliva and capillary blood concentrations that were approximately 10-fold and 100-fold greater, respectively, than those seen in serum or

TABLE 6–2 Progesterone Median Bioavailability Parameters Following Daily Application of 80 mg Progesterone Custom–Compounded Cream or Gel

	Cream			Gel			Cream/ Gel Paired Difference[a]	
	Median	25% Percentile	75% Percentile	Median	25% Percentile	75% Percentile	Median	*P*
Serum (*n* = 8)								
C_{max}, ng/mL	0.71	0.53	1.42	0.59	0.42	0.93	0.331	0.0781
T_{max}, ng/mL	9.00	5.00	14.00	8.00	3.50	10.00	1.00	0.6250
$AUC_{0-24\ h}$, ng h mL^{-1}	12.39	10.31	19.68	8.32	6.92	12.98	5.00	**0.0391**
Whole blood (*n* = 8)								
C_{max}, ng/mL	0.57	0.38	0.96	0.29	0.22	0.52	0.306	**0.0391**
T_{max}, ng/mL	8.00	5.00	16.00	7.00	3.00	10.00	1.50	0.2969
$AUC_{0-24\ h}$, ng h mL^{-1}	7.51	6.40	13.07	4.41	3.66	7.19	3.88	**0.0156**
Saliva (*n* = 7)								
C_{max}, ng/mL	8.71	4.13	12.07	7.36	2.42	8.14	2.63	0.4688
T_{max}, ng/mL	1.00	1.00	2.00	6.00	3.00	8.00	–4.00	0.0938
$AUC_{0-24\ h}$, ng h mL^{-1}	39.02	23.64	51.78	58.37	14.66	73.86	–11.97	0.6875
Capillary (*n* = 7)								
C_{max}, ng/mL	65.10	61.60	95.60	58.70	28.70	84.40	11.20	0.8125
T_{max}, ng/mL	8.00	1.00	24.00	8.00	4.00	12.00	2.00	0.4688
$AUC_{0-24\ h}$, ng h mL^{-1}	1,056	585	1,260	999	219	1,250	260	0.6875

[a] Values in bold show significant difference.

SOURCE: Du et al., 2013.

whole blood. It is unclear why there were large differences between whole blood and capillary blood progesterone concentrations. The high capillary blood and saliva concentrations may suggest optimal absorption and transport of progesterone to tissues from both compounded topical preparations (Du et al., 2013).

Considerations

Other researchers have commented on the disparity between progesterone concentrations in saliva and capillary blood, as compared to serum or whole blood. Based on current evidence, the therapeutic significance of higher progesterone concentrations in saliva and capillary blood is unclear (Ruan and Mueck, 2014). The effectiveness of percutaneous progesterone delivery in protecting the endometrium from unopposed estrogen is in question, mostly because of the very low serum progesterone concentrations achieved via that route of administration (Du et al., 2013; Ruan and Mueck, 2014; Stanczyk, 2014; Whelan et al., 2013; Wren et al., 2005). In a review article (Fugh-Berman and Bythrow, 2007), the authors compared the serum and plasma progesterone levels from topical progesterone creams from several studies (Burry et al., 1999; Carey et al., 2000; Cooper et al., 1998; Lewis et al., 2002; O'Leary et al., 2000) and found it was less than 5 ng/mL, the minimum level believed to induce secretory endometrium. Based on these findings and others, researchers suggest that serum or plasma progesterone concentrations should not be used as an index of tissue exposure of progesterone following topical progesterone cream therapy (Stanczyk, 2014).

Example Study 4: Compounded Estradiol, Progesterone, Testosterone, and DHEA Lozenge

Study Design and Results

Investigators have evaluated the pharmacokinetics of compounded estradiol, progesterone, testosterone, and DHEA in an open-label study in six postmenopausal women following dosing with a lozenge using the transbuccal route of administration (Wren et al., 2003b). Each lozenge, formulated by a compounding pharmacy (Bondi Junction, Australia) as a single batch, contained 17β estradiol (0.5 mg), progesterone (200 mg), testosterone (2.0 mg), and DHEA (10 mg), along with several excipients. Subjects administered one-half of a lozenge twice daily for 2 weeks, and the researchers measured hormone plasma and saliva concentrations over a 12-hour interval. Plasma and saliva concentrations of hormones were measured using validated radioimmunoassays. Substantial intersubject

variability in all hormone plasma concentrations were observed. In addition, concentrations in saliva were highly variable, especially following the first single dose, with ratios of saliva/plasma concentration of estradiol of more than 1,000. Data showed that the hormones were rapidly absorbed via the buccal mucous membrane, and peak plasma concentration of estradiol and progesterone were similar to the concentrations typically found in menstruating women.

Considerations

While the transbuccal route is a novel approach for administering steroid hormones to postmenopausal women, Wren et al. (2003b) noted the need for safety and efficacy studies to support the use of that particular route of administration. An earlier report (Miller et al., 2000) showed that sublingual administration of micronized estradiol and progesterone, with and without micronized testosterone, favorably decreases serum and urine markers of bone metabolism and prevents bone loss. Of note, the study medication was prepared at a local pharmacy from a single batch to avoid variability in hormonal content and composition of the sublingual tablets.

BIOAVAILABILITY OF TRADITIONALLY MANUFACTURED BIOIDENTICAL HORMONE THERAPY PRODUCTS

As discussed in Chapter 8 of this report, patients may not be aware of or understand that FDA-approved *bioidentical* hormone therapy (BHT) products exist and are readily available. As more FDA-approved forms of BHT products become available, some patient concerns about conventional hormone therapy may be allayed, and other therapy options (e.g., nonhormonal or conventional BHT) may have greater appeal (L'Hermite, 2017; Thompson et al., 2017). To serve as a reference point for the example studies discussed above, the following sections provide examples of bioavailability studies for traditionally manufactured bioidentical hormone products.

Reference Study on the Bioavailability of Traditionally Manufactured Bioidentical Progesterone Cream

Researchers at the Royal Hospital for Women in Randwick, Australia (Wren et al., 2003a) conducted a parallel, double-blind, randomized, placebo-controlled trial comparing the efficacy of percutaneous progesterone cream with a placebo cream. Seventy-two postmenopausal women completed the evaluation for vasomotor symptoms, blood lipid levels, bone metabolite markers, and quality of life. Subjects received 32 mg of progesterone in a cream (ProFeme, manufactured by Lawley Pharmaceuticals, Perth,

Australia)[8] or the same amount of cream containing no active ingredient. The cream was applied for a total of 12 weeks. While there was a significant increase in circulating serum progesterone by a median of 0.20 ng/mL, there was no detectable change in vasomotor symptoms, mood characteristics, sexual feelings, blood lipid levels, or bone metabolite markers.

Reference Study on the Bioavailability of FDA-Approved Bioidentical Estradiol and Progesterone Combination Product

On October 29, 2018, FDA-approved BIJUVA (estradiol and progesterone) capsules, the first FDA-approved BHT combination of estradiol and progesterone in a single, oral capsule for the treatment of moderate to severe vasomotor symptoms associated with menopause in women with a uterus.[9] As part of the approval process, the pharmacokinetics and oral bioavailability of a capsule combining 17β estradiol and progesterone was compared to those of widely used and approved separate formulations of estradiol and progesterone coadministered to healthy postmenopausal women (Pickar el al., 2015). Serial blood samples were collected, and the resulting plasma was used to measure unconjugated estradiol, total estrone, unconjugated estrone, and progesterone. Bioequivalence data supported the conclusion that the combination 17β estradiol and progesterone product demonstrated bioavailability similar to those of the respective reference products of estradiol and progesterone (Pickar et al., 2015).

CONCLUDING STATEMENTS

In summary, optimal bioavailability of an active ingredient in a compounded preparation is essential for exerting its intended pharmacological action. The paucity of bioavailability data from cBHT preparations is problematic and casts doubts on both safety and efficacy of these preparations. Even the small number of available clinical trials that attempted to evaluate bioavailability of cBHT lack the rigor of those conducted for FDA-approved BHT products.[10] Most of the existing studies do not have an active control and thus lack meaningful comparative data. In addition, most existing studies relied on the use of radioimmunoassays or methods used at clinical labs that are not as selective and specific as LC-MS/MS bioanalytical methods.

[8] Product information available at https://www.lawleybasecamp.com/media/pdf/pi-au/profeme-10-pi.pdf (accessed May 7, 2020).

[9] Product information available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210132s000lbl.pdf (accessed May 7, 2020).

[10] As a resource for general considerations for bioavailability studies, see https://www.fda.gov/media/121311/download (accessed May 7, 2020).

Conclusion 6-3

The paucity of reliable pharmacokinetic and bioavailability data for compounded bioidential hormone therapy (cBHT) preparations as compared to FDA-approved drug products, compromises the ability to evaluate the safety, efficacy, and product-to-product variability of cBHT preparations.

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7

The Safety and Effectiveness of Compounded Bioidentical Hormone Therapy

The primary charge to the committee is to assess the clinical utility of treating patients with compounded bioidentical hormone therapy (cBHT) preparations, which, as outlined in Chapter 1, requires an evidence-based examination of safety and effectiveness. In this chapter, the committee provides a narrative review of the relevant peer-reviewed evidence on the safety and effectiveness of cBHT and outlines the current framework for adverse event reporting, a critical component in assessing the safety of medications.

This chapter has a prioritized focus on bioidentical hormone therapy (BHT) preparations containing estrogens, progesterone, testosterone, dehydroepiandrosterone (DHEA), and pregnenolone. The committee recognizes that this prioritized list of bioidentical hormones may not be a comprehensive list of all ingredients used in cBHT preparations. In fact, there are other hormones (e.g., gonadotropin-releasing hormone), that are compounded to treat different hormone-related health conditions, but they are outside the scope of the committee's study. *However, the omission of a specific hormone or unique cBHT preparation from this chapter's review does not imply any level of safety, effectiveness, or potential usefulness.*

A large proportion of patients using cBHT appear to be women seeking treatment for menopausal symptoms and conditions, and indeed, of the limited number of studies that examine the safety and effectiveness of compounded preparations, the majority had research aims that focused on this patient population. As a result, the committee's conclusions focus on the use of cBHT to treat menopausal symptoms; however, evidence related to the safety and effectiveness of compounded testosterone in males is discussed where relevant. See Box 7-1 below for the medical indications for

BOX 7-1
FDA-Approved Hormone Therapy Indications

The natural aging process and the correlated decrease in steroid hormone levels are linked to symptomology associated with menopause and male hypogonadism. The use of hormone therapy products has been one way in which clinicians have sought to alleviate the symptoms brought on by the natural aging process.

Estrogen hormone therapy (either estrogen alone in the absence of a uterus or estrogen plus progesterone in the presence of a uterus) is FDA approved for treating the following four indications: (1) vasomotor symptoms; (2) genitourinary symptoms (vaginal atrophy); (3) bone loss prevention; and (4) hypoestrogenism induced by hypogonadism, primary ovarian insufficiency, or castration. Dehydroepiandrosterone (DHEA) hormone therapy has been FDA approved for treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, attributable to menopause. Testosterone hormone therapy is FDA approved for treating conditions associated with a deficiency or absence of endogenous testosterone in males. Pregnenolone is not an active ingredient in FDA-approved hormone therapy products.

SOURCES: FDA, 2020a; NAMS, 2017.

hormone therapy products approved by the U.S. Food and Drug Administration (FDA).

The chapter begins with a summary of the research strategy used to identify relevant data on safety and effectiveness. The summarized research strategy is followed by a narrative review of the committee's findings on the safety and effectiveness of various cBHT preparations, organized according to the bioidentical hormones reviewed. Next the committee outlines its conclusions related to the quality of evidence reviewed and the overall safety and effectiveness of cBHT preparations. The chapter closes with a short discussion on the role of adverse events reporting as a critical component of safety assessment.

RESEARCH STRATEGY

The committee conducted a literature search to identify a comprehensive body of evidence to inform its work. In coordination with one of the National Academies' senior research librarians, the committee constructed a literature search strategy that produced a broad range of research publications. A preliminary search queried six databases (Medline, Embase,

PubMed, Scopus, ClinicalTrials.gov, and Toxnet) for content related to the safety, effectiveness, and clinical utility of cBHT. Results from the search were limited to peer-reviewed articles published in the English language, including human, animal, and in vitro studies. The search was not limited by date of publication, but editorials, commentaries, letters, and notes were excluded. This search resulted in more than 16,000 articles. The committee decided to expand and restrict certain search terms in order to produce a more relevant literature base. With all other search parameters remaining the same, this second search provided more than 11,000 articles with potential relevance to the committee's charge. Of these articles, those that included the terms *compounding*, *compounded*, *bioidentical*, or *bioidentical*, and any of the committee's prioritized hormones in the title, keywords, or abstract were considered. Applying these criteria provided the committee with less than 50 articles relevant to the committee's charge.[1] For a more detailed description of the literature review and other data-gathering efforts performed by the committee, see Appendix B.

In addition to the formal literature searches, study stakeholders, including FDA, Professional Compounding Centers of America, representatives of select 503B outsourcing facilities, nonprofit professional organizations, and practicing medical prescribers of cBHT also submitted suggested articles and other references for the committee's review.[2] Furthermore, during the National Academies' external review process, additional articles were suggested by reviewers of the report. Based on the criteria described above, all relevant articles were added to the total body of collected peer-reviewed evidence.

The primary data collected in these searches had a specific focus on safety, effectiveness, and efficacy studies in humans. While the terms *effectiveness* and *efficacy* are similar, they are not the same. The effectiveness of a drug refers to its therapeutic effect in real-world settings. The efficacy refers to the therapeutic effect in controlled clinical settings—such as phase 2 or phase 3 randomized clinical trials. This difference is critically important.[3] Given the limited data on efficacy for cBHT preparations, the committee also considered clinical studies of effectiveness in their examination of clinical utility of cBHT preparations. Owing to its broader application to the body of research reviewed, the term *effectiveness* is used more generally across the chapter.

[1] There are a number of articles with relevance to multiple hormones. In their search efforts, the committee identified other published studies that have tangential relevance to the committee's charge; however, only the studies with greatest pertinence were reviewed in this report. As such, the reference list for this chapter represents the most relevant data and is not an inclusive list of all articles reviewed.

[2] Stakeholder submissions are available through the National Academies Public Access File.

[3] See Ernst and Pittler (2006) and Kim (2013) for an additional discussion.

To inform its research conclusions, from the mixed body of evidence produced by the literature review results, the committee prioritized the findings of systematic reviews and randomized controlled trials (RCTs), followed by relevant observational studies with large study populations. RCTs in particular are essential for studies of treatments intended to produce a therapeutic effect, given that measures of change over time can be influenced by many factors other than the actual treatment. Without the ability to compare to a treatment control group, observational studies rarely produce reliable estimates of treatment effects (CEBM, 2020). In addition to study type, the committee also considered the importance of methodological rigor. As such, small, low-quality cohort studies, case reports, and submitted anecdotal testimonies were reviewed to inform the committee's overall findings but are not formally summarized within the current chapter.

In its review of the literature, the committee recognized that the cBHT preparations used in the many of the research studies were formulated and dispensed by various types of pharmaceutical and health care facilities, details of which are not often clearly specified within the methods sections of the reviewed studies. To ensure that the committee's review of the literature met the Statement of Task's requirements, the committee focused its review on studies that examine the safety and effectiveness of cBHT preparations compounded in a 503A compounding pharmacy or 503B outsourcing facility. However, owing to the lack of such relevant studies, the committee's review also includes studies that used preparations compounded in governmental health care facilities, those compounded for use in academic research,[4] or in certain instances, those produced for studies that examined FDA-approved drug products with outcomes of interest that differ from the regulatory indication. In addition, because certain bioidentical hormones (i.e., estriol) are only manufactured and only approved for use outside of the United States, the committee reviewed select international studies to collect general findings related to the hormone's safety and effectiveness.

The committee identified a total of 13 studies related to cBHT that were of adequate methodologic rigor for inclusion in its review of safety and effectiveness of these preparations.[5] Table 7-1 provides an overview of these 13 studies, including a summary of their research objectives, findings, and reported adverse effects.

[4] Compounded drugs prepared for investigational new drug trials are subject to CGMP requirements under section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

[5] The committee was unable to identify any studies of adequate methodological rigor aimed at determining the safety and effectiveness of pregnenolone compounded preparations.

ESTROGENS AND PROGESTERONE COMPOUNDED PREPARATIONS

Effectiveness

The section below provides a summary of the studies that describe evidence related to the effectiveness of cBHT based on the known indications of FDA-approved drug products.[6] Estradiol has been shown to be one of the most effective hormone therapies for reducing vasomotor symptoms. However, based on the committee's review of the literature, including several systematic literature reviews, it appears that most of the evidence supporting this statement are based on the findings of safety and efficacy derived from clinical trials conducted by pharmaceutical companies during the FDA drug product approval process (L'Hermite, 2017; Marjoribanks et al., 2017; Stuenkel et al., 2015). Given that the effectiveness of estrogens is commonly assessed while in combination with progesterone, this section summarizes the committee's findings for both hormones.

Treatment of Vasomotor Symptoms

Based on their review, the committee could not identify any studies that could inform conclusions on the safety or effectiveness of compounded estrone or estradiol for the treatment of vasomotor symptoms. While there are RCT and observational studies to suggest that estriol (as manufactured and approved drug products outside of the United States) is effective in treating vasomotor symptoms (e.g., Ali, 2017; Foidart et al., 1991; Head, 1998), the study designs and small participant numbers of many of the studies do not provide enough evidence to suggest it is safer or more effective than FDA-approved hormone therapy products. Furthermore, as with the estradiol studies in the United States, the bulk of the evidence for estriol was collected by pharmaceutical companies seeking product approval in other countries.

For progesterone, a review by Whelan and colleagues (2012) identified three randomized, double-blind, placebo-controlled trials that evaluated the effectiveness of progesterone cream for the treatment of menopause-related vasomotor symptoms (Benster et al., 2009; Leonetti et al., 1999; Wren et al., 2003). Of the three studies, one used a compounded preparation (Leonetti et al., 1999), while the others used manufactured progesterone creams (see Table 7-1). The results from the 12-month study by Leonetti et al. (1999) had a low risk of bias and demonstrated a significant improvement in

[6] For additional discussion on labeled indications and contraindications for FDA-approved drug products, see Chapter 8, Table 8-1.

TABLE 7-1 Overview of 13 Studies Reviewed by the Committee with Relevance to the Safety and Effectiveness of cBHT

Author	Objective	Study Design	Population	Treatment
Dahir and Travers-Gustafson, 2014	Determine effect of DHEA on sexual health	Quasi-experimental pilot (4 weeks)	Women with breast cancer taking AI therapy *n* = 12 Race/ethnicity not reported Age (mean): 59.7 years	DHEA vaginal cream; 300 ug/daily

Other Notes	Measure	Main Outcomes Relevant to the Committee's Charge	Serious Adverse Events	Limitations
Exclusion criteria described	Female Sexual Function Index (FSFI) survey	Compared to baseline, improvements in individual domain scores of desire (P = 0.000), arousal (P = 0.002), lubrication (P = 0.018), orgasm (P = 0.005), satisfaction (P = 0.001), and pain (P = 0.000) No recurrence or progression of breast cancer over 3 years	Authors reported that no serious adverse events occurred	– Narrow time frame for enrollment and follow-up – Small sample size – Excluded surgical menopause under the age of 50 and women with recurrent *G. vaginalis* infection – Sexual functioning may have been affected by history or events such as relationship conflict, stress, or vacation – Absence of a randomized control group

continued

TABLE 7-1 Continued

Author	Objective	Study Design	Population	Treatment
Davis et al., 2018	Determine effect of testosterone on sexual satisfaction, vaginal symptoms	Randomized, double-blind, placebo-controlled (26 weeks)	Postmenopausal women taking an AI with VVA symptoms *n* = 44 Race/ethnicity not reported Age (mean): 57.7 years (treatment); 55.1 years (placebo)	Testosterone intravaginal cream; 300 ug/dose

Other Notes	Measure	Main Outcomes Relevant to the Committee's Charge	Serious Adverse Events	Limitations
Exclusion criteria described Treatment schedule: Daily for 2 weeks and then 3×/ week for 24 weeks	FSFI survey Female Sexual Distress Scale–Revised (FSDS-R), Profile of Female Sexual Function Questionnaire for UI Diagnosis; serum levels of sex sterioids	Greater improvements seen in treatment group in FSFI satisfaction scores ($P = 0.043$); FSDS-R scores ($P = 0.02$); sexual concerns ($P < 0.001$); sexual responsiveness ($P < 0.001$); vaginal dryness ($P = 0.009$); dyspareunia ($P = 0.014$) No between-group differences in serum levels of sex steroids at baseline or post-treatment No between-group differences in reported UI symptoms at 26 weeks, adjusted for baseline status	Authors did not report on adverse events for this study	– Higher dropout rate in control group – Low power to assess additional domains of sexual function – Recruitment was limited by patient concerns about the safety of hormone therapy after a diagnosis of breast cancer

continued

TABLE 7-1 Continued

Author	Objective	Study Design	Population	Treatment
Glaser et al., 2011	Determine effect of testosterone on somatic, psychological, and urogenital symptoms	Cohort (12 weeks)	Pre- and postmenopausal women *n* = 300 Race/ethnicity not reported Age (mean): 42.7 years (premenopausal); 53.0 years (postmenopausal)	Testosterone pellet (3.1 mm) – Initial dose varied across patient based on their weight (ranged from 75 mg to 160 mg) – Subsequent dose adjustments based on weight, avoidance of adverse events, and adequacy of clinical response

Other Notes	Measure	Main Outcomes Relevant to the Committee's Charge	Serious Adverse Events	Limitations
Exclusion criteria described	Menopause Rating Scale (MRS) Total scores and psychological, somatic, and urogenital subscale scores Health Related Quality of Life (HRQOL)	Premenopausal women: Higher testosterone doses correlated with greater improvement in MRS total score ($P < 0.05$) and urogenital subscore ($P < 0.01$) Higher testosterone doses did not correlate with greater improvement in either the psychological or somatic subscores ($P > 0.05$) Postmenopausal women: Higher testosterone doses correlated with greater improvement in MRS total score and all three subscores: somatic, psychological, and urogenital ($P < 0.001$)	Authors reported that no serious adverse events occurred	– Short-term study – Absence of a randomized control group or comparison group

continued

TABLE 7-1 Continued

Author	Objective	Study Design	Population	Treatment
Jankowski et al., 2006	Determine effect of DHEA on BMD and body composition	Randomized, double-blind, placebo-controlled (12 months)	Older men and women Participants were primarily White **Women** *n* = 70 (36 DHEA; 34 placebo) Age (mean): 68 years **Men** *n* = 70 (35 DHEA; 35 placebo) Age (mean): 69 years	Oral DHEA; 50 mg/daily
Kenny et al., 2010	Determine effect of DHEA and exercise on bone mass, strength, and physical function	Randomized, double-blind, placebo-controlled (6 months)	Women over 65 with DHEA levels < 550 ng/dL *n* = 99 (assigned) Particpants were primarily White Age (mean): 76.6 years	– Treatment arm 1: Oral DHEA 50 mg/d supplemented with yoga – Treatment arm 2: Oral DHEA 50 mg/d supplemented with aerobics – Control arm 1: Placebo supplemented with yoga – Control arm 2: Placebo supplemented with aerobics

Other Notes	Measure	Main Outcomes Relevant to the Committee's Charge	Serious Adverse Events	Limitations
Exclusion criteria described	BMD measured at baseline and 12 months	Men and women: Greater increase in BMD in DHEA group: Total hip (1.0%, *P* = 0.05), trochanter (1.2%, *P* = 0.06), and shaft (1.2%, *P* = 0.05) Women only: DHEA increased lumbar spine BMD (2.2%, *P* = 0.04; sex-by-treatment interaction, *P* = 0.05)	Placebo: One death (unrelated to study); one hospitalization for coronary artery stenting DHEA: One hospitalization for transient ischemic attack and one hospitalization for urinary tract infection	– Small sample size – Patient use of other reproductive steroids – Short duration of the therapy
Exclusion criteria described All received calcium and vitamin D supplements	BMD measured at baseline and 6 months	There were no significant changes in BMD or bone turneover markers between groups	Author did not report on adverse events for this study	– Small sample size – Short duration of therapy

continued

TABLE 7-1 Continued

Author	Objective	Study Design	Population	Treatment
Leonetti et al., 1999	Determine effect of progresterone on vasomotor symptoms, BMD	Randomized, double-blind, placebo-controlled (12 months)	Healthy women within 5 years of menopause *n* = 90 (assigned) All particpants were White Age (mean): 52 years	20 mg transdermal progesterone cream; applied daily

Other Notes	Measure	Main Outcomes Relevant to the Committee's Charge	Serious Adverse Events	Limitations
Exclusion criteria described All received daily multivitamins and 1,200 mg of calcium	– Weekly symptom diaries (self-report) – BMD measured in the lumbar spine, femoral neck, and hip	Symptoms: Greater self-reported improvement in vasomotor symptoms found in treatment group compared to placebo (83% versus 19%); ($P < 0.001$) BMD: No significant difference between group comparisons	Author did not report on adverse events for this study	– Limited consumer access to the custom-compounded preparation – Limited generalizability of research results

continued

TABLE 7-1 Continued

Author	Objective	Study Design	Population	Treatment
Mahmud, 2010	Determine effect of Bi-est, progesterone, testosterone, and/or DHEA on menopausal symptoms	Observational (average 30 month follow-up)	Postmenopausal women *n* = 189 (assigned) Race/ethnicity not reported Age (mean): 53.7 years	Treatment arm 1: transdermal Bi-est cream (estradiol 1 mg plus estriol 4 mg per gram) and sublingual progesterone (50–100 mg) and testosterone perivaginal cream – Participants began with a 0.5 gm twice daily dose of Bi-est cream, which was increased or decreasedas needed to control hot flashes and breast tenderness – Total testosterone was maintained around 25 ng/dl with dose adjustments as needed based on blood levels – Adjustments to progesterone doses were made to achieve blood levels close to 4 ng/ml

Other Notes	Measure	Main Outcomes Relevant to the Committee's Charge	Serious Adverse Events	Limitations
No exclusion criteria provided	Patient outcomes assessed over an average follow-up of 30 months Common symptoms assessed: hot flashes, night sweats, insomnia, lack of energy, low libido, and minor stiffness or achy joints	122 patients reported improvement in all common symptoms, 49 patients reported relief of most symptoms; 13 patients reported some improvements; 5 patients reported little to no improvement in symptoms	One patient was found to have an ER+ and PR+ breast cancer after 6 months of treatment Prior to joining this study the patient had been taking Premarin for 10 years, which the researchers believe may have caused the development of breast cancer in this patient	– Absence of a randomized control group – Lack of predetermined dosage formulation, participant outcomes, and statistical analysis of results – Multiple dosage forms of treatments (subset of patients switched from Bi-est cream to sublingual route)

continued

TABLE 7-1 Continued

Author	Objective	Study Design	Population	Treatment
Mahmud, 2010 (*continued*)				Treatment arm 2: Transdermal Bi-est cream (estradiol 1 mg plus estriol 4 mg per gram) and sublingual progesterone (50–100 mg) and DHEA – Participants began with a 0.5 gm twice daily dose of Bi-est cream, which was increased or decreased as needed to control hot flashes and breast tenderness – Adjustments to progesterone doses were made to achieve blood levels close to 4 ng/ml – Participants received DHEA if levels were determined to be low. Average dose began at 25 mg/day and was typically reduced to 25 mg every other day to maintain the desired level (approx. 120 μg/dl)

Other Notes	Measure	Main Outcomes Relevant to the Committee's Charge	Serious Adverse Events	Limitations

continued

TABLE 7-1 Continued

Author	Objective	Study Design	Population	Treatment
Morales, 1998	Determine effect effect of DHEA on steroid levels, body composition, and muscle strength	Randomized, double-blind, placebo-controlled crossover (12 months)	Older men and women **Women** *n* = 10 (assigned) Race/ethnicity not reported Age (mean): 54.5 years **Men** *n* = 9 (assigned) Race/ethnicity not reported Age (mean): 55.6 years	Oral DHEA; 100 mg/daily
Narkwichean et al., 2017	Determine effect effect of DHEA on in vitro fertilization (IVF) outcomes	Randomized, double-blind, placebo-controlled pilot trial (2 years)	Women receiving IVF with diminished ovarian reserves Treatment group: *n* = 27 All White British women Age (mean) = 36.8 years Placebo group: *n* = 25 84% White British women Age (mean) = 35.2 years	Oral DHEA; 75 mg/day; 12 to 20 weeks before starting ovarian stimulation

Other Notes	Measure	Main Outcomes Relevant to the Committee's Charge	Serious Adverse Events	Limitations
Exclusion criteria described 2 week washout period between crossover	BMD measured at baseline and 6 months	There were no significant change from baseline in the BMD of the hip and spine in men or women	Author reported that no serious adverse events occurred	– Small sample size
Exclusion criteria described Long protocol using hMG 300 IU/day	Number of oocytes retrieved; live birth rates; mRNA expression of developmental biomarkers in granulosa and cumulus cells	Treatment did not improve the response to controlled ovarian hyperstimulation or oocyte quality or live birth rate during IVF Treatment with long protocol in women predicted to have poor ovarian reserve	Author reported that no serious adverse reactions occurred	– No power calculation to determine sample size

continued

TABLE 7-1 Continued

Author	Objective	Study Design	Population	Treatment
Panjari et al., 2009	Determine safety of DHEA used to improve sexual function	Randomized, double-blind, placebo-controlled parallel group trial (52 weeks)	Postmenopausal women with low libido Race/ethnicity not reported Treatment group: *n* = 47 (assigned); age (mean) = 55.1 years Placebo group: *n* = 46 (assigned); age (mean) = 53.9 years	Oral DHEA; 50 mg/day

Other Notes	Measure	Main Outcomes Relevant to the Committee's Charge	Serious Adverse Events	Limitations
Exclusion criteria described	DHEA versus placebo on androgenic side effects, lipid profile, insulin–glucose homeostasis, and the endometrium were assessed over 52 weeks	DHEA did not significantly alter lipid profile or insulin sensitivity in postmenopausal women The pattern of breakthrough bleeding did not substantially differ between the DHEA and placebo groups, and no significant adverse endometrial effects were apparent	Author reported that no serious adverse events occurred	– Length of study is insufficient to have confidence in the reported endometrial safety outcomes – Endpoint for endometrial effects was not sufficiently powered

continued

TABLE 7-1 Continued

Author	Objective	Study Design	Population	Treatment
Virkki et al., 2010	Effect of DHEA on Sjorgren's syndrome-related fatigue	Multicentered, randomized, double-blind, placebo-controlled crossover trial (9 months)	Men and women with primary Sjorgren's Syndrome (reported as one group) *n* = 107 (including 7 men) Race/ethnicity not reported Age (range): 18–80 years	Oral DHEA; 50 mg/day

Other Notes	Measure	Main Outcomes Relevant to the Committee's Charge	Serious Adverse Events	Limitations
Exclusion criteria described 1 month washout period between crossover (two treatment groups lasting 4 months each)	General fatigue using the 20-item Multiple Fatigue Inventory (MFI-20); health-related, quality-of-life questionnaire	All of the MFI-20 subscales and the fatigue Visual Analog Scale showed improvements from baseline levels as a result of treatment ($P < 0.001$) No significant differences between placebo and DHEA treatment	Placebo treatement: One case of pneumonia and pneumococcal sepsis Other serious events resulting in patient dropout: (1) unilateral numbness, (2) suspected transient ischemic attack, and (3) exanthema DHEA treatment: Serious events resulting in patient dropout: muscle cramps in the calves and maculae on the back and cheek, (suspected as being discoid lupus erythematosus lesions)	– Owing to increased number of statistical analyses of the MFI-20s six subscale variables, there is an increased risk of analyses resulting in statistical siginicance by chance

continued

TABLE 7-1 Continued

Author	Objective	Study Design	Population	Treatment
Wiser et al., 2010	Effect of DHEA on IVF outcomes	Prospective, randomized, open-labeled, controlled trial (19 months)	Women with poor ovarian response to previous IVF cycles Race/ethnicity not reported Treatment group: *n* = 17; age (mean) = 36.9 years Control group: *n* = 16; age (mean) = 37.8 years	Oral DHEA; 75 mg/day, at least 6 weeks before starting first cycle of IVF ovulation Women who did not conceive took DHEA for at least 16–18 weeks

Other Notes	Measure	Main Outcomes Relevant to the Committee's Charge	Serious Adverse Events	Limitations
Exclusion criteria described All patients received long-protocol IVF	Estradiol levels, number of retrieved oocytes, quality and number of embryos, pregnancy and birth rate	Live birth rate for women in the DHEA group for both IVF treatment cycles = 23.1%; Live birth rate from women in the control group = 4.0% (P = 0.05)	Author reported that no serious adverse events occurred	– Small sample size – Outcomes may have been affected by variations in IVF protocol

continued

TABLE 7-1 Continued

Author	Objective	Study Design	Population	Treatment
Witherby et al., 2011	Effect of vaginal testosterone on estradiol and testosterone levels, and vaginal atrophy in breast cancer patients on aromatase inhibitors	Observational (28 days)	Women undergoing treatment with an AI in early stage breast cancer with reported vaginal itching, dryness, or dyspareunia Ethnicity not reported *n* = 20 (divided into two treatment groups); age (range): 45–69 years	Group 1 (*n* = 10): 300 ug intravaginal testosterone cream compounded with 13.5 mg of testosterone propionate Group 2 (*n* = 10): 150 ug intravaginal testosterone cream compounded with 6.75 mg of testosterone propionate

NOTE: AI = aromatase inhibitors; BMD = bone mineral density; DHEA = dehydroepiandrosterone; ER = estrogen receptor; FSDS-R = Female Sexual Distress Scale–Revised; FSFI = female sexual function index; IVF = in vitro fertilization; MRS = Menopause Rating Scale; MFI = Multiple Fatigue Inventory; PR = progesterone receptor: UI = urinary incontinence.

Other Notes	Measure	Main Outcomes Relevant to the Committee's Charge	Serious Adverse Events	Limitations
Exclusion criteria described	Assessment of hormone levels to confirm estradiol suppression Clinical effect based on analyses of serial questionnaire results Pathologic improvement of vaginal atrophy was analyzed based on a comparison of baseline and posttreatment maturation index, pH, and clinical examination	No significant difference in median serum estradiol levels before and after treatment ($P = 0.91$) No difference in posttreatment estradiol levels between dosing levels ($P > 0.99$) Significant improvement in mean total symptom score for vaginal atrophy ($P < 0.001$) and remained low at 1 month post-therapy ($P = 0.003$) No significant difference between dosing levels Posttreatment maturation values were significantly higher for 300-ug group ($P = 0.005$)	Author reported that no serious adverse events occurred	– Lack of a randomized control group – Recruitment of subjects was not systematic – Small sample size

vasomotor symptoms in the treatment group compared to placebo. However, Whelan et al. (2012) noted that owing to limited consumer access to the custom-compounded preparation and a reliance on self-reporting, there are limitations to the generalizability of the research results (see Table 7-1). The other two studies (manufactured progesterone product) were found to be no more effective than placebo in treating vasomotor symptoms (Benster et al., 2009; Wren et al., 2003).

Protection Against Bone Loss

Osteoporosis is a long and continuous process associated with aging and reduced gonadal function. The utility of estradiol in preventing osteoporosis by sustaining bone density has been well documented in multiple studies, and thus, bone loss prevention is an FDA label-indicated use for estradiol products (NLM, 2020). Based on its review, the committee was unable to identify any studies that could inform conclusions on the effectiveness of various formulations of compounded estrone or estradiol in preventing bone loss.

In a 1-year randomized double-blind, placebo-controlled trial, Leonetti et al. (1999) examined the effect of compounded transdermal progesterone on bone density and found no significant difference in the percentage increase in bone mineral density of the spine, femoral neck, and total hip between treatment and placebo groups (see Table 7-1).

Estriol is a less potent estrogen than estradiol and considered to be a relatively weak estrogen. Given the claims by certain advocates that estriol is a lower risk estrogen, the efficacy of estriol in combating bone mineral density loss, either alone or combined with a progestogen, has been the subject of multiple clinical investigations. Importantly, in the studies identified by the committee, the clinical investigations use treatments that are not compounded preparations, but are instead prescription products manufactured and approved for use outside of the United States. The overall results of these studies have been mixed, and none demonstrated that estriol is more effective than estradiol (example reviews: Ali, 2017; Cirigliano et al., 2007; Conaway, 2011; additional studies to consider: Devogelaer et al., 1998; Kika et al., 2009).

Treatment of Vaginal Atrophy (Genitourinary Syndrome)

Vaginal atrophy is associated with symptoms of vaginal dryness, itching, or pain, and is a common condition found in approximately 50 percent of postmenopausal women (Wysocki et al., 2014). This condition worsens with age and is one of the most common reasons for the use of hormone therapy in menopausal women. Based on its review, the committee was

unable to identify any studies that could inform conclusions related to the effectiveness of various formulations of compounded estrone, estradiol, estriol, or progesterone in the treatment of vaginal atrophy.

Research suggests that various estriol manufactured products are effective for the treatment of vaginal atrophy (Ali et al., 2017) and are approved for this indicated use in several countries outside of the United States (e.g., Synapause, Estriel). However, of the studies identified by the committee, only two compared the effectiveness of estriol with estradiol. One of these studies, a 12-week, open-label, parallel-group RCT with active control compared the efficacy of a 2 mg micronized estradiol-releasing silicone rubber vaginal ring (product manufactured outside of the United States; releasing 6.5 to 9.5 µg per 24 hours; n = 112) to a 0.5 mg estriol-releasing vaginal pessary (product manufactured and approved outside of United States; n = 53)[7] in treating symptoms of vaginal atrophy in postmenopausal women (Henriksson et al., 1994). The estradiol product appeared more effective than the estriol product at preventing vaginal atrophy, and patients who previously used vaginal pessaries reported a strong preference for the estradiol-releasing vaginal ring.

A similar 12-week, open-label, parallel-group RCT with active control study compared the efficacy of an 2 mg estradiol-releasing vaginal ring[8] (FDA-approved drug product; releasing 7.5 µg per 24 hours; n = 72) to an 1 mg estriol vaginal cream (product manufactured and approved outside of United States; 0.5 administered daily for 2 weeks followed by 0.5 administered three times weekly; n = 66)[9] in alleviating vaginal dryness (Barentsen et al., 1997). Both treatments produced similar improvements in vaginal health, but in the crossover phase of this study, found that women preferred the estradiol-releasing vaginal ring over the estriol cream.

Safety

The section below provides a summary of the studies that describe evidence related to the safety of cBHT based on the known indications of FDA-approved drug products.[10] Estradiol is a common active ingredient in hormone therapy. However, based on the committee's review of the literature, many of its findings on the potential risks related to estradiol treatment are derived from clinical trials designed to explore estradiol safety

[7] Ovesterin, approved drug product in Sweden (https://vardgivarwebb.regionostergotland.se/Startsida/Verksamheter/Regiondirektor/Rad-och-kommitteer-/Lakemedel-new/Rekomenderade-Lakemedel/Gynekologi11).

[8] Estring, FDA-approved drug product (NLM, 2020).

[9] Synapause, approved drug product in the Netherlands (WHO, 2018).

[10] For additional discussion on labeled indications and contraindications for FDA-approved drug products, see Chapter 8, Table 8-1.

in clinical trials conducted by pharmaceutical companies during the FDA drug product approval process (L'Hermite, 2017; Marjoribanks, et al., 2017; Stuenkel et al., 2015). Given that the safety of estrogens is commonly assessed while in combination with progesterone, this section summarizes the committee's findings for both hormones.

Risk of Breast Cancer

The committee was unable to identify research studies that could inform conclusions on the safety of various formulations of compounded estrone, estradiol, estriol, or progesterone related to risk of developing breast cancer. Given that a lack of evidence does not imply safety, below, the committee provides a brief overview of findings based on the examination of potential risks attributed to FDA-approved drug products or drug products manufactured and approved for use outside of the United States.

Results from primarily large observational studies suggest there may be an increased risk of developing breast cancer associated with unopposed use of estradiol, but by combining estradiol therapy with micronized progesterone this risk may be lessened (Asi et al., 2016; L'Hermite 2017; Stute, 2018). Furthermore, in comparison to synthetic progestins and estradiol therapy, combined micronized progesterone and estradiol therapy has been shown to lessen the risk of breast cancer (Asi et al., 2016; Stute, 2018). In addition, estrogen therapy is contraindicated in breast cancer survivors because of the potential to increase the odds of cancer reoccurring (L'Hermite, 2017; Moegele et al., 2013; Ortmann et al., 2011). Although it has been suggested that vaginal delivery of low-dose estradiol or estriol is a safe option for hormone receptor-positive breast cancer patients treated with aromatase inhibitor therapy, the data are limited to a few small observational studies (Dew et al., 2003; Pfeifer et al., 2011).

Risk of Endometrial Cancer

Safety studies have identified endometrial cancer as a clearly associated risk with use of unopposed estrogen therapy in women with an intact uterus, and that this risk is effectively decreased when the estrogen is taken in combination with adequate doses of a progestogen (Smith, 1975; Stuenkel, 2015). The committee was unable to identify research studies that could inform conclusions on the safety of various formulations of compounded estrone, estradiol, estriol, or progesterone related to risk of developing endometrial cancer. However, as mentioned in Chapter 5 and 6, it can be assumed that if a compounded medication is erroneously formulated or dosed, certain intended effects, such as protective factors, may be not be achieved.

Certain studies have suggested that estriol may pose a lower risk for promoting endometrial cancer by acting as an antagonist to block the endometrial neoplastic effects of estradiol and estrone; however, these research conclusions are debated in the field (see reviews: Ali et al., 2018; Cirigliano, 2007). Furthermore, studies suggest that providing the correct route of administration, dose, and length of treatment are critical factors in the hormones' endometrial stimulatory effects. For example, one meta-analysis of 12 studies (Vooijs and Geurts, 1995) determined that intravaginal estriol treatment at recommended doses did not produce endometrial proliferation, even after treatment lasting a maximum of 2 years.

Data from a population-based, case–control study of endometrial cancer in postmenopausal women suggest that oral estriol increases the relative risk of endometrial cancer and atypical hyperplasia, while only weak associations were observed between vaginal formulations of low potency estrogens and relative risk of developing endometrial cancer (Weiderpass et al., 1993). Given the wide range of marketed dosage forms for compounded estriol preparations, these are important details for prescribers to consider.

Risk of Venus Thromboembolism

Venus thromboembolism is also associated with the use of oral estrogen therapy. Although studies have shown a clear association between the use of unopposed estradiol and the risk of stroke, multiple reviews suggest that combining progesterone with estradiol therapy can help to prevent a stroke from occurring (Bath, 2005; Cobin et al., 2017; L'Hermite, 2017; Oliver-Williams, 2019; Renoux, 2010). In addition, the risk for venous thromboembolism may be decreased when using transdermal estrogen therapy as opposed to oral estrogen (Canonico, 2008; Mohammed, 2015).

The committee was unable to identify research studies that could inform conclusions on the effect of various formulations of compounded estrone, estradiol, estriol, or progesterone on the risk of developing venus thromboembolism. However, as mentioned above and throughout this report, if a compounded medication is erroneously formulated or dosed, certain intended effects, such as protective factors, may be not be achieved.

Conclusion 7-1

There is limited and mixed quality evidence to suggest that estriol may be effective in treating certain menopausal symptoms; however, there is insufficient evidence to inform conclusions regarding the safety of estriol. Well-designed and properly controlled clinical trials are needed to clarify the potential clinical utility of estriol.

Conclusion 7-2

There is insufficient evidence to determine the safety and effectiveness of compounded estriol in comparison to bioidentical hormone therapy products approved by FDA or similar international bodies.

TESTOSTERONE THERAPY IN MEN

Testosterone is widely used by middle-aged and older men. However, it is only FDA approved for men who suffer from male hypogonadism resulting from an associated medical condition, such as a failure of the testicles to produce testosterone because of genetic factors or chemotherapy treatment. As an FDA-approved drug product, the efficacy of testosterone products in men is supported by numerous high-quality randomized and placebo-controlled studies, including studies examining its effectiveness for off-label use (Mohler et al., 2018; Roy et al., 2017; Santoro et al., 2016; Snyder et al., 1999, 2016, 2017; Storer et al., 2017).[11] The committee was unable to identify relevant studies that could inform conclusions regarding the safety and effectiveness of various formulations, doses, and dosage forms of compounded testosterone for FDA-approved indications in men.

Effectiveness

Testosterone treatments of men with hypogonadism caused by a medical condition have been approved on the basis of their effects on testosterone levels, without any studies of clinical efficacy in this population. Beneficial

[11] At the time this report was written, testosterone was available by prescription in eight FDA-approved drug products for hormone therapy in males for conditions associated with symptoms of deficiency or absence of endogenous testosterone. These products could be prescribed in one of the following forms: gel, transdermal patch, buccal system tablet, and pellet (see Chapter 5 for additional information on hormone products).

effects observed in other men taking FDA-approved testosterone products include increased muscle mass and grip strength, heightened libido and increased sexual activity, resolution of mild anemia, and increased bone density (Roy et al., 2017; Snyder et al., 1999, 2016, 2017; Storer et al., 2017).

A number of other effects, not in the list of FDA-approved indications, have been observed. Small decreases in total, HDL, and LDL cholesterol, and fasting insulin have been found in an RCT (Mohler et al., 2018). Other reported effects, including weight loss, delayed development of type 2 diabetes, enhanced recovery from stroke, and reduced risk of venous thrombosis, prostate cancer, major cardiovascular events, and overall mortality have been claimed on the basis of observational studies but have not been confirmed in RCTs.

Safety

Prostate Cancer Risk

Testosterone increases levels of prostate-specific antigen (PSA) in men, but long-term studies required to assess increased risk of prostate cancer have not been conducted. Men considered at elevated risk of prostate cancer associated with family history or elevated PSA levels are generally advised to avoid taking supplemental testosterone treatment (Santoro et al., 2016).

Cardiovascular Risks

Data on the risk of cardiovascular events are mixed. A number of observational studies have suggested that there are benefits of testosterone therapy, but a few clinical trials have indicated potential harm (Basaria et al., 2010; Budoff et al., 2017). Because of these contradictory findings, FDA has asked manufacturers of testosterone gels to conduct a large, long-term study to address this issue of cardiovascular safety. This study is currently under way (ClinicalTrials.gov NCT03518034).

Other Potential Risks

Other warnings and precautions noted on FDA-approved drug product labels include urinary symptoms, azoospermia, sleep apnea, gynecomastia (an enlargement or swelling of breast tissue in males), and erythrocytosis (excessive red blood cell production) (FDA, 2020a). Virilization can occur in women and children with secondary exposure to testosterone (FDA, 2020a).

TESTOSTERONE THERAPY IN WOMEN

As discussed in earlier chapters of the report, there is interest in the use of testosterone treatment for women; however, currently there are no FDA-approved drug products with indications to treat health conditions in women. As a result, high-quality evidence on the effects of testosterone in women is more limited than the evidence for men.

Effectiveness

Sexual Health

Several randomized studies have shown that compounded testosterone treatment improved libido and increased sexual activity in menopausal women who had previously reported diminished sexual desire or satisfaction (Dahir and Travers-Gustafson, 2014; Davis, 2018; Glaser et al., 2011; Islam et al., 2019; see Table 7-1). Similar findings were found in studies that used manufactured testosterone (Shifren et al., 2006; Simon et al., 2005).

A consensus statement on the use of testosterone therapy for women, developed and endorsed by major professional societies focusing on endocrinology, women's health, and menopause, supports the findings that testosterone therapy can improve sexual function in postmenopausal women, but cautions that the dose administered should approximate physiological testosterone concentrations in premenopausal women (Davis et al., 2019).

Menopause-Related Symptoms

Other studies suggest compounded testosterone may be effective in treating vaginal atrophy and other menopausal symptoms (Glaser et al., 2011; Witherby et al., 2011; see Table 7-1). As noted earlier in the chapter, however, these are largely uncontrolled studies, and outcomes related to the treatment of symptoms are difficult to interpret as improvement in symptoms can be influenced by many factors other than treatment administered. No well-controlled studies have demonstrated benefit of treatment with compounded testosterone preparations for menopausal symptoms.

Safety

Breast Health

The role of testosterone in breast growth and breast cancer risk are highly debated within the field and, at present, there are insufficient

long-term data from controlled studies to support conclusions regarding potential benefits and risks (Davis, 2019; Glaser et al., 2019; Kotsopoulos and Narod, 2012).

Other Potential Risks

Studies of short-term use of testosterone in women have not uncovered any major safety concerns, but they have noted hair growth and acne as adverse effects (Achilli et al., 2017; Islam et al., 2019). Long-term safety data are lacking.

DHEA THERAPY

DHEA is a precursor to testosterone and estrogen that is known to decrease as people age. Although sometimes compounded into hormone therapy preparations, DHEA is also sold as commercially available supplements. Often the methodical sections of studies fail to adequately describe the origins of DHEA used in studies, which presents a challenge for accurately assessing the safety and effectiveness of the hormone in cBHT preparations. Therefore, unless specifically identified as a compounded preparation, the committee considered the hormone to be a commercially available supplement.

Effectiveness

Sexual Health

The only FDA-approved DHEA product (Intrarosa) is a vaginal insert used to treat moderate to severe pain in women during sexual intercourse (NLM, 2020). However, systematic reviews, and a 2019 consensus position statement published by professional societies with a focus on women's health, concluded that systemic DHEA is not associated with improvements in sexual desire or function among postmenopausal women whose adrenal function is normal (Davis et al., 2011, 2019; Elraiya et al., 2014).

Cognitive Function and Mental Health

A 2006 review of six studies addressed the use of DHEA supplementation for cognitive function in healthy men and women over age 50 (Evans et al., 2006). This review concluded that data from controlled trials do not support the claims of a beneficial effect of DHEA supplementation on cognitive function in this population. Another systematic review of randomized, placebo-controlled trials evaluating the effect of DHEA on depression found a significant positive effect of DHEA supplementation (Peixoto et al., 2018).

Bone Loss

Reported outcomes on DHEA's effectiveness on bone density have been mixed. Although a few studies have reported marginally significant effects on bone density (Jankowski et al., 2006), other studies have not (Kenny et al., 2010; Morales et al., 1998; see Table 7-1).

Other Potential Effects

Additional health outcomes of DHEA use include effects on physical performance and fatigue, insulin resistance, and fertility problems. Other small RCTs found no fatigue-related effects of compounded DHEA therapy in Sjögren's syndrome patients with a DHEA deficiency (Virkki et al., 2010; see Table 7-1) and a decrease in insulin resistance in older men and women (Weiss et al., 2011). One small RCT, conducted over a period of 2 years, found no significant benefits to physical performance, insulin sensitivity, or quality of life in elderly women or men treated with DHEA (Nair, 2006).

A small RCT on women with diminished ovarian reserves who were not responding well to in vitro fertilization and who were given compounded DHEA were found to have improved embryo quality and higher live birth rates compared to untreated controls (Wiser et al., 2010; see Table 7-1). A somewhat larger study using compounded DHEA found no significant improvement in live birth rates in women undergoing in vitro fertilization (Narkwichean, 2017; see Table 7-1), and a review published in 2015 found a possible increase in the chance of live birth in women receiving DHEA but noted that when studies that appeared to be at high risk of bias were excluded from the analysis, no such effect was found (Nagels et al., 2015).

Safety

In contrast to the extensive literature investigating the effectiveness of DHEA therapy, there is scant literature to support the safety of DHEA use in men or women. Most of the current data on DHEA safety have been derived from adverse events reported in trials such as those discussed above. However, in a placebo-controlled, double-blinded RCT examining the safety of daily DHEA, Panjari and colleagues (2009) reported findings of no adverse endometrial effects (see Table 7-1). More randomized data is needed to determine if DHEA use is associated with other conditions such as breast cancer and cardiovascular disease (Davis et al., 2011; Elraiyah et al., 2014).

cBHT RESEARCH CHALLENGES

Although bioidentical hormones are used in both FDA-approved and compounded preparations, the dose and combination of ingredients used in compounded preparations depend on the formulation chosen by the prescriber and/or compounding pharmacist (see Chapter 5 for an additional discussion on this topic). As a result of the countless permutations of cBHT formulations, evidence supporting the safety and effectiveness of compounded hormone preparations is limited to the specific combinations of hormones, inactive ingredients, and formulation chosen by the research team conducting the study.

Often, compounding pharmacies combine multiple hormones into a single formulation; however, the evidence to support the effectiveness or safety of these formulations is scant.[12] One prospective cohort study examined the effects of transdermal cBHT formulations containing estriol, progesterone, DHEA, and testosterone on 75 postmenopausal women (Stephenson et al., 2013). Improvements were noted in climacteric symptoms, measures of quality of life, and selected cardiovascular biomarkers. Study limitations included the absence of randomization and the small, community-based participant sampling, which limits the power and generalizability of the study results.

In another observational study, researchers examined the effect of transdermal Bi-est cream and sublingual progesterone and either testosterone or DHEA on the relief of common menopausal symptoms (hot flashes, night sweats, insomnia, lack of energy, low libido, and minor stiffness or achy joints) (Mahmud, 2010). Authors reported improvements in all symptoms in 122 out of 189 participants. Study limitations included an absence of randomization and appropriate control groups, and the use of multiple cBHT dosage forms (18 patients switched from transdermal to sublingual dosage forms) throughout the course of the study (see Table 7-1).

As a final example, in one observational study, which included 200 women 18 years of age or older, participants received a cBHT prescription including multiple hormones following consultation services. The researchers reported reductions in vasomotor, anxiety, sleep disturbances, and other quality-of-life symptoms in women who received sublingual formulations, while topical formulations were associated with more modest reductions in symptoms. However, the absence of randomization and use of participant-specific dosing regimens with no control group for comparison

[12] For a further discussion on the compounded hormone preparations and their use, see Chapters 5 and 8.

limits the types of conclusions that can be drawn about the effectiveness of these formulations (Ruiz and Daniels, 2014).[13]

SUMMARY OF RESEARCH FINDINGS

In its review of the evidence, the committee determined there is a dearth of high-quality research with a primary or secondary endpoint focused on the safety, effectiveness, and performance of cBHT preparations. Many of the studies had severe methodological limitations, the most common being the lack of standardized measures (e.g., assessments of hormone level, randomizations, participant exclusion and inclusion criteria, reporting measures) and minimal details on participant-specific dosing regimens, formulations, and dosage forms of the treatment, and where relevant, control arms of the study. The variability of cBHT formulations and research methodologies not only affects the quality of the evidence used to support research conclusions, but it also minimizes the ability to compare results among studies or apply meta-analytic methods to draw conclusions from a larger number of patients (Boothby et al., 2004). The committee recognizes that for the large patient population using cBHT, it is difficult, if not impossible, for clinicians to provide evidence-based guidance on the safety and effectiveness of each unique formulation. That being said, safety and effectiveness data are still required for understanding the risks-to-benefit ratio for all medications, which is fundamental to the practice of medicine in this country.

[13] Although this study is a large observational study, the participant specific dosing regimens prevent the committee from creating a table that could accurately capture the published data.

Conclusion 7-3

There is a dearth of high-quality evidence—data from studies that would meet FDA's requirements for granting regulatory approval to a drug product—available to establish whether compounded bioidentical hormone therapy preparations are safe and effective for their prescribed uses.

Conclusion 7-4

Well-designed and properly controlled clinical trials are needed to provide reliable evidence about the safety and effectiveness of compounded bioidentical hormone therapy preparations.

Conclusion 7-5

The majority of marketing claims about the safety and effectiveness of compounded bioidentical hormone therapy preparations, whether in absolute terms or in comparison to FDA-approved bioidentical hormone therapy, are not supported by evidence from well-designed, properly controlled studies.

ADVERSE EVENT REPORTING FOR cBHT

In addition to the data acquired through high-quality, well-controlled research studies, adverse event data are also critical for characterizing the safety of a medication. Adverse drug events are defined by FDA as "any unanticipated experience or side effect associated with the use of a drug or therapeutic biologic in humans, whether or not it is considered related to the product" (FDA, 2020b). Adverse events range from minor symptoms to permanent disability and death. The Centers for Disease Control and Prevention (CDC) regularly tracks the number of emergency department visits attributed to adverse events and has reported that they are responsible for approximately 1.3 million emergency department visits annually by adults (CDC, 2017a) and 200,000 visits by children and adolescents (CDC, 2017b).

Adverse Event Identification

Clinical trials assessing drug efficacy are a required component of FDA's drug approval process and provide insight into the drug's safety as well. Following the FDA's Physician Labeling Rule, adverse events identified during preapproval clinical trials must be described in product labeling. The critical information listed in a drug's labeling is intended to inform practitioners' benefit–risk analysis when making prescribing decisions in concert with their patients (FDA, 2013).

Although 503B outsourcing facilities are not required to comply with FDA's labeling regulations applicable to approved drugs, they must prepare a modified label that includes some of the labeling requirements such as a list of active and inactive ingredients and the drug dosage form and strength. However, 503A compounding pharmacies are not subject to any specific labeling requirements (FDA, 2018). In the absence of evidence to the contrary, boxed warnings for compounded hormones are similar to those in FDA-approved drug products.

Reporting Systems

Because the clinical trials conducted to support drug approval—which are often conducted for short periods of time in highly selected populations of patients—cannot fully characterize a drug's safety profile, FDA requires that all "[c]ompanies with approved applications for drugs and therapeutic biologics as well as manufacturers, packers and distributors listed on product labels … submit postmarketing safety information to FDA" (FDA, 2020b). FDA also extends the requirements for postmarketing safety reporting to "companies marketing unapproved prescription drugs or over-the-counter drugs as well as retailers whose name appears on the product label as a distributor" (FDA, 2020b). These adverse events are collected in the FDA Adverse Events Reporting System (FAERS), which can be publicly searched and subject to analysis.[14]

Under section 503B(b)(5) of the Federal Food, Drug, and Cosmetic Act, an outsourcing facility must submit adverse event reports to FDA "in accordance with the content and format requirements established through guidance or regulation under Section 310.305 of Title 21, Code of Federal Regulations (or any successor regulations)." Section 310.305 requires, among other things, that manufacturers, packers, and distributors of marketed prescription drug products that are not the subject of an approved

[14] See FDA's Guidance for Industry, Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act, October 2015. See https://www.fda.gov/media/90997/download (accessed May 15, 2020).

new drug application or an abbreviated new drug application, to establish and maintain records of all serious, unexpected adverse drug experiences associated with the use of their prescription drug products, and to make these reports available to FDA. In addition, those subject to mandatory reporting regulations must maintain records of all adverse events for 10 years, including "raw data and any correspondence relating to the adverse event" (FDA, 2015). However, these requirements do not apply to 503A compounding pharmacies, which therefore are not required to submit reports for any known or suspected adverse events.

MedWatch is another component of adverse event reporting. MedWatch permits submission of reports of adverse events or other problems with products by anyone—patients as well as health professionals—using Form 3500. Patients can contact an FDA consumer complaint coordinator to assist them in submitting a report (FDA, 2016).

In addition to the reporting systems, data is collected through the peer-reviewed literature or pilot research and case studies presented at professional meetings. For example, FAERS data collected from peer-reviewed articles describe adverse events that resulted from excessive dosages of estrogen, progesterone, and testosterone caused by the unpredictable delivery of hormones from compounded pellets (Foreman et al., 2010). In addition, preliminary data presented by Dr. Daniel Jiang at recent North American Menopause Society annual meetings describes increased incidences of abnormal uterine bleeding and hysterectomies in postmenopausal women treated with compounded pellet hormonal therapy, as compared to those treated with FDA-approved pellets (Jiang, 2017, 2018).

Adverse Event Data for cBHT

At the request of the committee, FDA shared FAERS cases on cBHT.[15] Reported events included incidences of overdosing (often related to the treatment of gender dysphoria), hormone withdrawal symptoms experienced by children after second-hand exposure to bioidentical estrogens and androgens, and compounding errors. One example of an adverse drug effect caused by medical error relates to an allergic reaction to propylene glycol in a product, which had erroneously been labeled as propylene glycol free. The quality of sterile drugs used in injected or implanted formulations were also identified as the source of localized infections occurring in patients. Pellet extrusions were

[15] These adverse event reports were identified in the FAERS database by the study sponsor—FDA. FDA identified adverse events reports that relate to the use of a cBHT by reading through report descriptions of all entries marked as compounded. It is important to note that there may be other FAERS cases related to the use of a cBHT, but if the necessary indication box for compounded medications was not checked during the data entry process, then those cases would not be represented in the full data set.

also identified as a source of localized infections. One side effect reported by many women included nausea and vomiting, which is a common side effect of exposure to high dose estrogens (FDA, 2019b). Because cBHT preparations contain the same active ingredients as FDA-approved BHT products, there are similar risks of adverse events at equivalent dosages. However as noted in Chapter 6, cBHT inconsistencies in compounded formulations can increase the risk of bioavailability-related adverse reactions.

Underreporting of Adverse Events

Underreporting of adverse drug events related to prescribed drugs is common. Underreporting may be attributable to confusion as to the actual cause of the adverse event. Many physicians and patients may not know that an adverse outcome is caused by a drug, and when they do, often do not think to report that outcome to FDA or the manufacturer (Kesselheim et al., 2019). Underreporting may also occur because individual patients and physicians are not required to make such reports.

Nonetheless, adverse event reporting is important to advance knowledge about drug safety. According to QuarterWatch, an independent analysis of the quarterly release of FDA MedWatch data, essentially all safety signals identified by FDA come from analysis of the FAERS Quarterly Data Extract Files rather than direct reporting from 503A and 503B facilities. In the wake of recommendations by the Institute of Medicine in 2000 to expand adverse event reporting systems, some states created their own systems to work in parallel with the FDA reporting requirements. However, a 2015 report revealed that only 28 states had systems for reporting adverse events (Hanlon et al., 2015).

Underreporting of adverse events related to compounded drugs may be more extensive than for FDA-approved drugs. First, while manufacturers of FDA-approved drugs are required to report adverse events that they learn about, 503A compounding pharmacies are not required to report adverse events. Second, parallel state systems do not fill this gap. A survey in 2015 found that only 30 percent of states (13 out of the 43 that responded) require sterile compounding facilities to report serious adverse events (The Pew Charitable Trusts, 2016). Third, underreporting is driven by manufacturers' disincentives to reveal their own products as potentially unsafe. For example, 503B outsourcing pharmacies—unlike 503A compounding pharmacies—are required to report adverse events to FDA. But in 2018, FDA inspectors visiting a 503B outsourcing facility discovered a company-owned data file containing more than 4,000 unreported adverse events that occurred between 2013 to 2018 (FDA, 2019a). While the bulk of these reports were considered minor adverse drug events, more than 300 were serious adverse drug events (see Table 7-2). These events should have

TABLE 7-2 Adverse Events Discovered During an FDA Inspection

Adverse Event	Number of Events Identified
Breast cancer	154
Deep vein thrombosis	40
Heart attack	37
Stroke	31
Prostate cancer	25
Endometrial cancer	21
Pellet extrusions	2,335
Cellulitis	529
Hair loss	30
Acne	11
Facial hair	7
Enlarged clitoris	6
Voice deepening	2
Amenorrhea	1
Other complications	427

SOURCE: FDA, 2019a.

been reported no more than 15 days after they were identified. In addition to being a violation of FDA regulations, the failure to report these events hinders the ability for researchers to identify data patterns that could signal specific safety issues (FDA, 2019b).

Importance of Drug Safety Surveillance

Although the industries required to comply with adverse event reporting regulations often consider them to be burdensome, the data they provide are part of the system that can help inform patients about drug safety. In recent decades, advances in technology have opened new pathways to search for such safety signals through other data sources through claims databases, clinical trial data databases (e.g., ClinicalTrials.gov), and social media. Data collected from the FAERS database have been a valuable component of this network to help understand the root causes of adverse events. It is therefore critical that all known and suspected adverse drug events are reported.

Conclusion 7-6

There are concerns with the voluntary and incomplete nature of adverse events reporting for compounded preparations. The lack of an easily accessible safety database limits assessment of the frequency, type, and severity of adverse events related to the use of compounded bioidentical hormone therapy. Improved monitoring of adverse events are required to characterize the safety of these compounded preparations.

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8

The Use of Compounded Bioidentical Hormone Therapy

In Chapter 1, the committee defined *clinical utility* as a multidimensional construct that not only reflects evidence about safety and effectiveness but also therapeutic need and patient preference.[1] To address portions of the study's overall charge, this chapter reviews the available evidence related to patients' therapeutic need, preference, and overall *use* of compounded bioidentical hormone therapy (cBHT) preparations. To inform its work, the committee reviewed relevant data from the limited peer-reviewed literature; collected testimonies from patients, clinicians, and compounding pharmacists; and considered submitted data from key stakeholders. In its review, the committee focused on current patterns and trends of cBHT use and looked to identify factors that appear to influence patient interest. As a framework for this discussion, the chapter begins with a brief overview of the rise of cBHT and rationales for use, and it follows with a discussion on the assessed therapeutic need for cBHT, derived from evidence-based clinical guidance that inform practice.

As discussed within the chapter, cBHT medications are marketed to treat a broad spectrum of indications related to patient health and well-being. Given the limitations of the study's scope, timeline, and resources, the chapter has a narrowed scope and predominant focus on the evidence related to the claims and the use of cBHT to treat menopausal symptoms. Limited discussions with respect to use in men or for other indications are included where relevant.

[1] In the context of this report, *therapeutic need* relates to the treatment of menopausal and male hypogonadism symptoms.

THE WOMEN'S HEALTH INITIATIVE: IMPACT ON THE CURRENT USE OF HORMONE THERAPY

Findings from the Women's Health Initiative

In the 1990s, the Women's Health Initiative (WHI), a comprehensive prospective, multiethnic study, was launched to examine whether menopausal hormone therapy (MHT) might prevent the development of heart disease, as well as to assess overall health risks and benefits of select U.S. Food and Drug Administration (FDA)-approved hormone therapy (Hays et al., 2003; Stefanick et al., 2003). The MHT component of WHI was a long-term, randomized controlled trial (RCT) examining health outcomes that emerged after treating more than 27,000 healthy postmenopausal women either with placebo or the most commonly prescribed oral hormone replacement regimens at that time: Premarin (conjugated estrogens alone) or Prempro (conjugated estrogens combined with medroxyprogesterone acetate) (Rossouw et al., 2002; WHI, 2020).[2,3]

Since the launch of the study, research published more than 100 findings related to a broad spectrum of health risks and benefits for the use of hormone therapy in postmenopausal women (WHI, 2020). An interim analysis of the study results revealed an excess risk for coronary heart disease and stroke, breast cancer, and venous thromboembolic events for participants in the combined therapy (Prempro) arm (Rossouw et al., 2002).[4] As a result, the RCT was terminated early. Although the estrogen-only treatment arm did not demonstrate an increased risk of breast cancer after 7 years, it did show a similar increase in stroke and a smaller increase in blood clots, particularly in the first 2 years of use. As a result, FDA issued requirements for all estrogen/progestin or estrogen-only hormone therapy products to contain a boxed warning on the potential serious adverse events associated with long-term administration (Stefanick, 2005). See Appendix H to review boxed warnings for bioidentical hormone therapy (BHT) products containing estrogens and testosterone.

After the termination of WHI, additional subgroup analyses were conducted showing that women in the youngest age group (50 to 59 years old) were at lowest risk for adverse outcomes. Indeed, the trial produced evidence of a potentially protective effect for those younger women

[2] The WHI Hormone Therapy Trials included 27,347 women ages 50–79. The enrolled women were followed during active treatment versus placebo (5.6 years in the estrogen-plus-progestin trial, 7.2 years in the estrogen-alone trial), and for an extended period with no treatment. The total follow-up period for the study was 13 years.

[3] Conjugated estrogens are a blend of estrogen sulfates purified from pregnant mares' urine.

[4] There were also treatment benefits of therapy reducing risk of fractures and colorectal cancer rates (Rossouw et al., 2002).

treated with conjugated estrogens alone, compared to those who received a placebo, for coronary heart disease, cancer, and all-cause mortalities in the 18-year cumulative follow-up analysis (Manson and Kaunitz, 2016; Manson et al., 2017). Given these modified findings demonstrated the greatest harm occurred in women over age 60 or 10 or more years beyond menopause, the leading menopause societies revised their practice guidelines.

The revised guidelines moved away from a one-size-fits-all recommendation that treatment should be for the shortest duration and at the lowest possible dose to one that allows for greater flexibility and individualized treatment (ACOG, 2014; de Villiers et al., 2016; NAMS, 2017). By 2016, the Endocrine Society's revised statement on menopause hormone therapy reflected a more positive stance:

> With updated data analysis suggesting the safety of MHT in younger postmenopausal women, most now agree that MHT is a highly effective and safe intervention to treat symptoms in the early menopause years. (Santoro et al., 2016)

Regarding long-term hormone therapy, the U.S. Preventive Services Task Force (USPSTF) recently reconfirmed its recommendation against using hormone therapy to prevent chronic medical conditions in postmenopausal women (USPSTF, 2019). Additionally, the online service Uptodate.com, a respected resource for evidence-based clinical guidance, recommends against the use of hormone therapy to treat menopause-associated osteoporosis, except in rare exceptions, or for more than 5 years in healthy women (Barbieri, 2019).

Effect of WHI on Perceptions and Treatment Options for Hormone Therapy

FDA-Approved Bioidentical Hormone Therapy

Early analyses and science communication efforts for WHI, coupled with FDA's limited indications for use and requirements for boxed warnings of potential adverse effects, had a lasting effect on clinician- and patient-related concerns regarding the use of hormone therapy (Barlow, 2014; Thompson et al., 2017). The post-WHI era also served as the impetus for a "serious reevaluation" by pharmaceutical companies for alternative options to treat menopausal symptoms, including the use of "bioidentical"

hormones (Stefanick, 2005).[5] As a result, the following years saw an expansion of FDA-approved bioidentical estrogen and progesterone products, in lower doses, and different routes of administration (FDA, 2020).

Despite the expanded selection of lower dosages and routes of administration of FDA-approved bioidentical hormone products made available following the release of the initial WHI findings, there were only modest gains in use rates for vaginal hormone preparations (Constantine et al., 2019a). In fact, there was a nationwide decline in filled prescriptions for either oral or transdermal FDA-approved bioidentical hormone products from 2002 to 2009, with an estimated 75 percent decrease for oral products and 25 percent decrease for transdermal products (Ettinger et al., 2012), as compared to the rates of use prior to the release of the WHI results. This decline in use led to suggestions that other competing factors were at play (Constantine et al., 2019b), including the parallel increase in the use of cBHT. An analysis of the Surveillance, Epidemiology, and End Results Program database from 1975 through 2014 suggested that the post-2002 rise in endometrial cancer rates in parallel with the decrease in use of approved estrogen-progestogen therapies was likely attributable to an increase in cBHT use, and to a lesser degree, the increasing prevalence of obesity and diabetes (Constantine et al., 2019b). Researchers noted that cBHT use is not systematically tracked and that the magnitude of its use was not definitively known.

cBHT

As discussed in Chapter 2, compounded medications are traditionally formulated to offer therapeutic alternatives for patients with unique medical needs that cannot be met by available FDA-approved BHT products (FDA, 2018; USP, 2015). Compounding can also fill gaps in cases of FDA-approved BHT product shortages and discontinuations (Glassgold, 2013). However, as reviewed in Chapter 5, FDA has reviewed and approved the sale of dozens of different BHT products, offering a selection of different doses and forms to address the diverse therapeutic needs of patient populations. Given the availability of FDA-approved bioidentical hormone products, *the question remains, why do certain patients and providers use cBHT in lieu of available FDA-approved drug products?*

[5] A bioidentical hormone is a hormone that is chemically and structurally identical to one produced by the human body, with the implication that an identical structure translates to an identical physiologic response as endogenous hormones. Bioidentical hormones may be synthesized from plant or animal sources, or completely chemically synthesized, and are offered as FDA-approved drug products or as preparations that have not undergone FDA approval. See Chapter 4 for an additional discussion on this topic.

BIOIDENTICAL HORMONE THERAPY: INDICATIONS FOR USE

Informed by published guidance from the American Medical Association (2016), the committee created a figure that describes available options for "use" of FDA-approved BHT products and nonapproved cBHT preparations to treat menopausal symptoms. The committee structured its consideration of cBHT use with attention to evidence-based clinical guidance (see Figure 8-1).

Traditionally, patients see a physician prescriber (or nonphysician prescriber in certain situations) who evaluates their symptoms and medical history. Prescribers can then discuss treatment options from the perspectives of safety, efficacy, and medical need specific to the patient at hand. As illustrated in box 1 of the top pathway in Figure 8-1, physicians can prescribe an FDA-approved drug product, with the prescriber informed by evidence-based labeled indications, safety and efficacy, and clinical practice guidance. The FDA-approved drug product label gives the physician prescriber and the patient information about indications, contraindications, warnings, side effects, dosing, and monitoring. In addition, boxed warnings are included for all FDA-approved drug products that include estrogen or testosterone (FDA, 2015; Stefanick, 2005).

As illustrated in Box 2 in Figure 8-1, clinicians can prescribe an FDA-approved BHT product for indications that are "off-label."[6] In this situation, the prescriber can be informed by clinical guidance and data on the safety and efficacy for the FDA-approved labeled indications. For the purpose of this report, off-label prescribing is either (1) for an indication that is not included in the product labeling, (2) at a dosage outside the recommended range, (3) uses a different route of administration, or (4) for a patient from a population not listed on the labeled recommendation (e.g., pediatric) (AMA, 2016). Approximately10 percent to 20 percent of all prescriptions are for off-label use, with a much higher rate in some medical specialties (e.g., oncology, pediatrics, and rare diseases). Similar to medical guidance for cBHT prescribing, off-label prescribing should be limited to use that is supported by scientific evidence (AMA, 2016). As discussed in Chapter 7, the use of testosterone to treat female sexual dysfunction is a relevant example of off-label prescribing of an FDA-approved BHT product (AMA, 2016; Davis et al., 2019).

In other circumstances, many of which are not tracked, clinicians can prescribe nonFDA-approved cBHT for their patients. As noted in Box 3 of Figure 8-1, there are typically two reasons to prescribe cBHT: (1) to provide a medication in an alternate dose or form, or (2) to omit components of an

[6] FDA does not regulate the practice of medicine and therefore does not regulate the use of off-label prescribing (21 U.S.C. § 396).

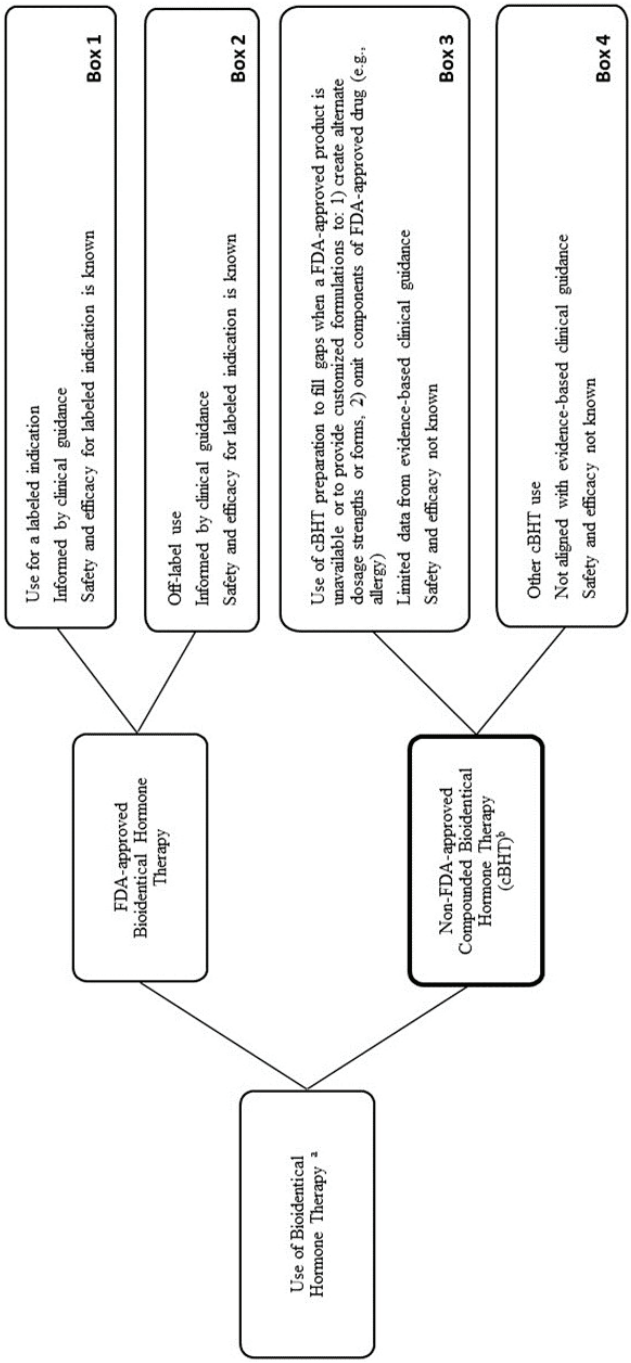

FIGURE 8-1 Use of bioidentical hormone therapy.
[a] This figure does not represent all possible uses of FDA-approved drug products or cBHT preparations.
[b] The use of non-FDA-approved cBHT is the prioritized focus of the current chapter.
SOURCE: Concept from AMA, 2016.

FDA-approved drug product (e.g., allergy). As noted in Chapter 7, there is insufficient evidence to establish whether cBHT preparations are safe or efficacious for their prescribed uses.

Box 4 of Figure 8-1 relates to "other use of cBHT" that goes beyond the historical rationale for compounded drug use. Similar to the situation in Box 3, there is insufficient evidence to establish whether cBHT preparations are safe or efficacious for their prescribed uses, but in addition, "other use of cBHT" does not align with evidence-based clinical guidance. (See the section "Professional Guidance and Clinical Practice Guidelines for the Use of cBHT" for an additional discussion.)

Purported Indications for the Use of cBHT

The vast majority of FDA-approved BHT products have labeled indications related to treating moderate to severe vasomotor symptoms and vulvovaginal atrophy of menopause in women and testosterone deficiency or hypogonadism in men (Crandall, 2019; NLM, 2020; Shifren et al., 2019; see Table 8-1 for a list of labeled indications).[7] In direct contrast to the short list of indications for FDA-approved BHT products, there are a substantial number of purported indications for the use of cBHTs. Marketed claims for cBHT include, but are not limited to, the treatment of conditions related to antiaging (e.g., longer, fuller hair and smoother skin), sexual health, joint pain, general chronic pain, insomnia, cardiovascular diseases, and various mental health disorders.[8] In addition, researchers have identified certain cBHT preparations marketed for long-term use that is not supported by the available safety evidence (Conaway, 2011). As noted in Chapters 3 and 7, cBHT preparations do not go through the FDA approval process, and they lack robust empirical evidence on their safety and efficacy to treated marketed indications.[9] In general, the contraindications for cBHT might, at a minimum, be expected to be similar to those of similar FDA-approved BHT products. (See Table 8-1 for a list of labeled contraindications.) However, it is unknown whether, and if so how, these and other concerns are communicated to patients.

To better understand which special populations of patients use cBHT, in addition to or in lieu of FDA-approved drug products, the committee

[7] Access to FDA drug labels is available on the National Library of Medicine's (NLM's) DailyMed online database at https://dailymed.nlm.nih.gov/dailymed/spl-resources-all-drug-labels.cfm (accessed May 7, 2020).

[8] Example cBHT indications for use were collected from submitted resources from stakeholders (see Appendix A); public statements from consumers, clinicians, and pharmacists (see Appendix A); and peer-reviewed literature (e.g., McPherson et al., 2019; Yuksel et al., 2017).

[9] See Chapter 7 for a review of the safety and effectiveness of commonly formulated cBHT preparations.

TABLE 8-1 Common Indications and Contraindications for FDA-Approved Bioidentical Hormone Therapy Products

Bioidentical Hormone	Brand Name	Preparation	Label Indications
17β-estradiol	Estrace	Pill	Moderate to severe vasomotor symptoms; moderate to severe symptoms of vulvar and vaginal atrophy; hypoestrogenism due to hypogonadism, castration, or primary ovarian failure; prevention of osteoporosis
17β-estradiol	Alora	Patch	Moderate to severe vasomotor symptoms; moderate to severe symptoms of vulvar and vaginal atrophy; hypoestrogenism due to hypogonadism, castration, or primary ovarian failure; prevention of osteoporosis
17β-estradiol	Climara	Patch	Moderate to severe vasomotor symptoms; moderate to severe symptoms of vulvar and vaginal atrophy; hypoestrogenism due to hypogonadism, castration, or primary ovarian failure; prevention of osteoporosis
17β-estradiol	Vivelle-Dot	Patch	Moderate to severe vasomotor symptoms; moderate to severe symptoms of vulvar and vaginal atrophy; hypoestrogenism due to hypogonadism, castration, or primary ovarian failure; prevention of osteoporosis
17β-estradiol	Minivelle	Patch	Moderate to severe vasomotor symptoms; prevention of osteoporosis
17β-estradiol	Menostar	Patch	Prevention of osteoporosis
17β-estradiol	Estrogel	Gel	Moderate to severe vasomotor symptoms; moderate to severe symptoms of vulvar and vaginal atrophy

Contraindications
Undiagnosed vaginal bleeding; Known, suspected, or history of breast cancer; Known or suspected estrogen-dependent neoplasia; Active deep vein thrombosis, pulmonary embolism, or history of these conditions; Liver dysfunction or disease; Known or suspected pregnancy; Active or recent (e.g., within the past year) arterial thromboembolic disease; Known sensitivity to FD&C Yellow No. 5 (tartrazine)
Undiagnosed vaginal bleeding; Known, suspected, or history of breast cancer; Known or suspected estrogen-dependent neoplasia; Active deep vein thrombosis, pulmonary embolism, or history of these conditions; Liver dysfunction or disease; Known or suspected pregnancy; Active or recent (e.g., within the past year) arterial thromboembolic disease; Known hypersensitivity to product or its ingredients
Undiagnosed vaginal bleeding; Known, suspected, or history of breast cancer; Known or suspected estrogen-dependent neoplasia; Active deep vein thrombosis, pulmonary embolism, or history of these conditions; Liver dysfunction or disease; Known or suspected pregnancy; Active or history of arterial thromboembolic disease; High risk of venous thrombosis or arterial thrombosis; Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders
Undiagnosed vaginal bleeding; Known, suspected, or history of breast cancer; Known or suspected estrogen-dependent neoplasia; Active deep vein thrombosis, pulmonary embolism, or history of these conditions; Liver dysfunction or disease; Known or suspected pregnancy; History of arterial thromboembolic disease; Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders; Known hypersensitivity to product or its ingredients
Undiagnosed vaginal bleeding; Known, suspected, or history of breast cancer; Known or suspected estrogen-dependent neoplasia; Active deep vein thrombosis, pulmonary embolism, or history of these conditions; Liver dysfunction or disease; Known or suspected pregnancy; History of arterial thromboembolic disease; Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders; Known hypersensitivity to product or its ingredients
Undiagnosed vaginal bleeding; Known, suspected, or history of breast cancer; Known or suspected estrogen-dependent neoplasia; Active deep vein thrombosis, pulmonary embolism, or history of these conditions; Liver dysfunction or disease; Known or suspected pregnancy; History of arterial thromboembolic disease; Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders
Undiagnosed vaginal bleeding; Known, suspected, or history of breast cancer; Known or suspected estrogen-dependent neoplasia; Active deep vein thrombosis, pulmonary embolism, or history of these conditions; Liver dysfunction or disease; Known or suspected pregnancy; History of arterial thromboembolic disease; Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders; anaphylactic reaction or angioedema with product

continued

TABLE 8-1 Continued

Bioidentical Hormone	Brand Name	Preparation	Label Indications
17β-estradiol	Elestrin	Gel	Moderate to severe vasomotor symptoms
17β-estradiol	Divigel	Gel	Moderate to severe vasomotor symptoms
17β-estradiol	Estrace	Vaginal cream	Moderate to severe vulvar and vaginal atrophy due to menopause
17β-estradiol	Estring	Vaginal ring	Moderate to severe vulvar and vaginal atrophy due to menopause
17β-estradiol	Evamist	Spray	Moderate to severe vasomotor symptoms
17β-estradiol	Imvexxy	Vaginal tablet	Moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause
Estradiol cypionate	Depo-estradiol	Injection	Moderate to severe vasomotor symptoms; hypoestrogenism due to hypogonadism

Contraindications
Undiagnosed vaginal bleeding; Known, suspected, or history of breast cancer; Known or suspected estrogen-dependent neoplasia; Active deep vein thrombosis, pulmonary embolism, or history of these conditions; Liver dysfunction or disease; Known or suspected pregnancy; History of arterial thromboembolic disease; Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders; anaphylactic reaction or angioedema with product
Undiagnosed vaginal bleeding; Known, suspected, or history of breast cancer; Known or suspected estrogen-dependent neoplasia; Active deep vein thrombosis, pulmonary embolism, or history of these conditions; Liver dysfunction or disease; Known or suspected pregnancy; History of arterial thromboembolic disease; Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders; Known hypersensitivity to product or its ingredients; anaphylactic reaction or angioedema with product
Undiagnosed vaginal bleeding; Known, suspected, or history of breast cancer; Known or suspected estrogen-dependent neoplasia; Active deep vein thrombosis, pulmonary embolism, or history of these conditions; Liver dysfunction or disease; Known or suspected pregnancy; History of arterial thromboembolic disease; Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders; anaphylactic reaction or angioedema with product
Undiagnosed vaginal bleeding; Known, suspected, or history of breast cancer; Known or suspected estrogen-dependent neoplasia; Active deep vein thrombosis, pulmonary embolism, or history of these conditions; Liver dysfunction or disease; Known or suspected pregnancy; History of arterial thromboembolic disease; Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders; Known hypersensitivity to product or its ingredients; anaphylactic reaction or angioedema with product
Undiagnosed vaginal bleeding; Known, suspected, or history of breast cancer; Known or suspected estrogen-dependent neoplasia; Active deep vein thrombosis, pulmonary embolism, or history of these conditions; Liver dysfunction or disease; Known or suspected pregnancy; History of arterial thromboembolic disease; Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders; anaphylactic reaction or angioedema with product
Undiagnosed vaginal bleeding; Known, suspected, or history of breast cancer; Known or suspected estrogen-dependent neoplasia; Active deep vein thrombosis, pulmonary embolism, or history of these conditions; Liver dysfunction or disease; History of arterial thromboembolic disease; Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders; anaphylactic reaction or angioedema with product
Undiagnosed vaginal bleeding; Known, suspected, or history of breast cancer; Known or suspected estrogen-dependent neoplasia; Active deep vein thrombosis, pulmonary embolism, or history of these conditions; Liver dysfunction or disease; Known or suspected pregnancy; Recent (e.g., within the past year) arterial thromboembolic disease; Known hypersensitivity to product or its ingredients

continued

TABLE 8-1 Continued

Bioidentical Hormone	Brand Name	Preparation	Label Indications
Micronized progesterone	Prometrium	Pill	Prevention of endometrial hyperplasia in nonhysterectomized postmenopausal women who are receiving conjugated estrogens tablets; also indicated for use in secondary amenorrhea
Micronized progesterone	Crinone	Vaginal gel	Supplementation or replacement as part of an assisted reproductive technology (ART) treatment for infertile women with progesterone deficiency (8%); secondary amenorrhea (4% and 8%)
Micronized progesterone	Prochieve	Vaginal gel	Supplementation or replacement as part of an assisted reproductive technology (ART) treatment for infertile women with progesterone deficiency (8%); secondary amenorrhea (4% and 8%)
Micronized progesterone	Endometrin	Ovules	To support embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an assisted reproductive technology (ART) treatment program for infertile women
17β-estradiol and micronized progesterone	Bijuva	Pill	Moderate to severe vasomotor symptoms due to menopause
Testosterone	Testim	Gel	Indicated for replacement therapy in males for conditions associated with symptoms of deficiency or absence of endogenous testosterone
Testosterone	Vogelxo	Gel	Indicated for replacement therapy in males for conditions associated with symptoms of deficiency or absence of endogenous testosterone
Testosterone	Androgel	Gel	Indicated for replacement therapy in males for conditions associated with symptoms of deficiency or absence of endogenous testosterone

Contraindications
History of arterial thromboembolic disease; Undiagnosed abnormal genital bleeding; Known, suspected, or history of cancer of the breast; Active deep vein thrombosis, pulmonary embolism, or history of these conditions; Liver dysfunction or disease; Known or suspected pregnancy; History of arterial thromboembolic disease
Undiagnosed vaginal bleeding; Liver dysfunction or disease; Known or suspected malignancy of the breast or genital organs; Missed abortion; Known sensitivity or hypersensitivity to product or its ingredients
Undiagnosed vaginal bleeding; Liver dysfunction or disease; Known or suspected malignancy of the breast or genital organs; Missed abortion; Known sensitivity or hypersensitivity to product or its ingredients
History of arterial thromboembolic disease; Known allergic reaction; Undiagnosed vaginal bleeding; Liver dysfunction or disease; History of arterial thromboembolic disease; Known or suspected malignancy of the breast or genital organs; Ectopic pregnancy or missed abortion; Known allergic reactions
Undiagnosed vaginal bleeding; Known, suspected, or history of breast cancer; Known or suspected estrogen-dependent neoplasia; Active deep vein thrombosis, pulmonary embolism, or history of these conditions; Liver dysfunction or disease; Known or suspected pregnancy; History of arterial thromboembolic disease; Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders; Known hypersensitivity to product or its ingredients; anaphylactic reaction or angioedema with product
Carcinoma of the breast or known or suspected carcinoma of the prostate; pregnancy or breastfeeding
Carcinoma of the breast or known or suspected carcinoma of the prostate; pregnancy or breastfeeding
Carcinoma of the breast or known or suspected carcinoma of the prostate; pregnancy or breastfeeding; pregnant women need to be aware of the potential for transfer of testosterone from men

continued

TABLE 8-1 Continued

Bioidentical Hormone	Brand Name	Preparation	Label Indications
Testosterone	Fortesta	Gel	Indicated for replacement therapy in males for conditions associated with symptoms of deficiency or absence of endogenous testosterone
Testosterone	Natesto	Nasal gel	Indicated for replacement therapy in males for conditions associated with symptoms of deficiency or absence of endogenous testosterone
Testosterone	Androderm	Patch	Indicated for replacement therapy in males for conditions associated with symptoms of deficiency or absence of endogenous testosterone
Testosterone	Striant	Tablet (buccal system)	Indicated for replacement therapy in males for conditions associated with symptoms of deficiency or absence of endogenous testosterone
Testosterone	Testopel	Pellet	Indicated for replacement therapy in males for conditions associated with symptoms of deficiency or absence of endogenous testosterone
Testosterone cypionate	Depo-Testosterone	Injection	Indicated for replacement therapy in males for conditions associated with symptoms of deficiency or absence of endogenous testosterone
Dehydro-epiandrosterone (DHEA; also known as Prasterone)	Intrarosa	Vaginal insert	Indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause

NOTE: This table is limited to products that include only those active ingredients identified in the committee's Statement of Task at the time of publication.
SOURCE: NLM, 2020.

submitted a data request to the editor-in-chief of the *International Journal of Pharmaceutical Compounding* (IJPC), Loyd Allen, for a review of all cBHT-related articles published in the IJPC from 1997 to 2018. As summarized in a presentation to this committee on June 27, 2019, Allen noted that special populations using cBHT include patients who cannot tolerate certain components of FDA-approved drug products (e.g., lactose), need

Contraindications
Carcinoma of the breast or known or suspected carcinoma of the prostate; pregnancy or breastfeeding
Carcinoma of the breast or known or suspected carcinoma of the prostate; pregnancy or breastfeeding
Carcinoma of the breast or known or suspected carcinoma of the prostate; pregnancy or breastfeeding
Carcinoma of the breast or known or suspected carcinoma of the prostate; pregnancy or breastfeeding
Carcinoma of the breast or known or suspected carcinoma of the prostate; pregnancy or breastfeeding
Carcinoma of the breast or known or suspected carcinoma of the prostate; pregnancy or breastfeeding; known hypersensitivity to the drug; serious cardiac, hepatic, or renal disease
Undiagnosed abnormal genital bleeding: Any postmenopausal woman with undiagnosed, persistent or recurring genital bleeding should be evaluated to determine the cause of the bleeding before consideration of treatment

alternate dosage strengths or forms (e.g., for those who have difficulty swallowing solids), or need preparations to support treatment compliance (e.g., in cases where convenience or personal preference is important). In the latter case, Allen cited the following reasons: compounds providing individualized flavors, ease of transporting and administration, combinations of drugs not otherwise obtainable, and those that are easily modifiable for

individual patients. Unfortunately, no specific examples were provided to better understand the applicability directly to cases regarding the use of cBHT to support a medical need. Allen did, however, note that children and the elderly would especially benefit from some of these important capabilities, though these are subpopulations not likely to be relevant for hormone therapy to treat menopausal symptoms.After initial research efforts, the committee identified a need to obtain additional clarity on evidence-based support for the use of cBHT to treat menopausal symptoms. To address this need, the committee reviewed available evidence-based clinical guidance issued by professional medical organizations.

PROFESSIONAL GUIDANCE AND CLINICAL PRACTICE GUIDELINES FOR THE USE OF cBHT

Overall Perspectives

As part of evidence-based medical practice, clinical guidance has a growing role for improving clinical decision making and potentially patient outcomes (IOM, 2011). In collaboration with the National Academies' senior librarians, the committee conducted a search of large, global research databases and other online sources to identify published statements and professional guidance relevant to the committee's charge. Databases searched included Embase, Medline, PubMed, Scopus, and Google. In this effort, the committee prioritized the findings of professional guidance issued by nonprofit medical societies, professional associations, or other evidence-based clinical resources.

In general, the collected statements expressed concerns regarding the quality, safety, and effectiveness of compounded preparations and cautioned against their use if FDA-approved BHT product options were available. In fact, in each of the professional guidance statements reviewed by the committee, FDA-approved BHT products were recommended as the first-line hormone therapy treatments (see Table 8-2 for relevant excerpts from clinical guidance).[10]

At the same time, many of the clinical guidance statements, such as the 2017 position statement on hormone therapy by the North American

[10] Additional public statements issued by medical societies, professional associations, and women's health advocacy organizations were reviewed but are not outlined in the chapter. Table 8-2 provides a non-comprehensive list of clinical guidance that represents the overall findings of the committee. For example, other statements, such as those issued by the American Association of Clinical Endocrinologists (www.aace.com), the National Women's Health Network (nwhn.org), and Our Bodies, Ourselves (ourbodiesourselves.org) also express concerns related to the safety and effectiveness of cBHT preparations (Cobin and Goodman, 2017; Pearson, 2019; NWHN, 2020).

TABLE 8-2 Professional Medical Guidance on Use of cBHT

Organization Name	Year	Concerns and Recommendations
American College of Obstetricians and Gynecologists (ACOG)	2018	"Patients should be counseled that menopausal hormonal therapies that are proved to be safe and effective by the FDA are more appropriate for their use than individual pharmacy-compounded preparations." "Patients should be educated on the FDA approval status of compounded preparations and their risks and benefits, including the risks specific to compounding." "Physicians should exercise caution in prescribing compounded hormones when FDA-approved alternatives exist." (ACOG, 2018, p. 4)
American Medical Association (AMA)	2016	"Some clinics that provide services for transgender individuals recommend compounded hormone therapy preparations made by compounding pharmacies such as topical testosterone and estradiol creams for cost-saving purposes, since many of the necessary drug therapies are not covered by insurance. There is no evidence that custom compounded hormone therapy products are safer or more effective than FDA-approved therapies." (AMA, 2016, p. 9, lines 48–50, and p. 10, lines 1–2) "Our AMA: (1) recognizes the term 'bioidentical hormone' as a marketing term not grounded in science; use of the term 'compounded hormone therapy' is preferred; (2) will urge that renewed attention be devoted to purity and potency of compounded hormone therapy formulations; (3) will urge continued attention to the mandatory reporting of adverse events related to the use of compounded hormone therapies; (4) recommends that physicians and other prescribers fully inform patients of the potential side effects and risks of the use of compounded hormone replacement therapy; and (5) will request that when drug ingredients with black box warnings are used in compounded products, patients should be informed about the warnings and precautions associated with the use of such drug ingredients." (CSAPH Report 4-I-16, Recommendation to amend Policy D-120.969) (AMA, 2016, p. 13)

continued

TABLE 8-2 Continued

Organization Name	Year	Concerns and Recommendations
Endocrine Society	2019	"Since the final hormone formulations of most compounding pharmacies are not subject to FDA monitoring for dose, purity, safety, or efficacy, there may be additional and at this point unknown risks associated with them." "Nonetheless, compounded hormones are sometimes offered at a lower cost than FDA-approved preparations, and this can motivate patients to request them." "The Society supports FDA regulation and oversight of all hormones regardless of chemical structure or method of manufacture. This should include, but not be limited to, the following: Surveys for purity and dosage accuracy; Mandatory reporting by drug manufacturers of adverse events; A registry of adverse events related to the use of hormone preparations; Inclusion of uniform information for patients, such as warnings and precautions, in packaging of hormone products." (Endocrine Society, 2019, p. 2)
Global Consensus Position Statement on the Use of Testosterone Therapy for Women	2019	"Compounded 'bioidentical' testosterone therapy cannot be recommended for the treatment of hypoactive sexual drive disorder, due to the lack of evidence for efficacy and safety, unless an authorized equivalent preparation is not available (Expert opinion). In the absence of an available approved product, if a compounded product is needed, the compounding pharmacy should be compliant with purity of Active Pharmaceutical Ingredients (API) and Good Manufacturing Practice (GMP) to meet industry standards for quality and safety. Dosing should be limited to achieving testosterone concentrations in the physiologic premenopausal range." (Davis et al., 2019, p. 4, Recommendation 12(d))
International Menopause Society	2016	"Women requesting compounded BHT should be encouraged to consider regulated products containing hormones which are structurally identical to those produced in the body. These are available in a wide range of doses and delivery methods." "Prescribing of compounded BHT is not recommended due to the lack of quality control and regulatory oversight associated with these products, together with lack of evidence of safety and efficacy." (Baber et al., 2016, p. 134)

TABLE 8-2 Continued

Organization Name	Year	Concerns and Recommendations
North American Menopause Society (NAMS)	2017	"Compounded bioidentical HT should be avoided, given concerns about safety, including the possibility of overdosing or underdosing, lack of efficacy and safety studies, and lack of a label providing risks." "If compounded bioidentical HT is prescribed, concerns about safety should be discussed, and the indication for prescribing compounded rather than government-approved bioidentical HT should be documented (allergy, medical need for lower-than-available dose, different preparation)." (NAMS, 2017, p. 744, Recommendation III(a))
UpToDate	2019	"Many women have turned to compounded 'bioidentical' hormone therapy as an alternative to conventional hormones for treating symptoms of menopause. 'Bioidentical' means that the hormones used for therapy are identical in molecular structure to the hormones produced by the ovaries. 'Compounded' means the preparation is mixed in a special compounding pharmacy in order to create a customized dose of hormones in the form of pills, creams, or vaginal suppositories." "The quality of these custom compounded products is not regulated by the U.S. Food and Drug Administration (FDA), and the dose of hormones can vary from batch to batch. For these reasons, expert groups caution against using them." (Barbieri, 2019)

SOURCES: ACOG, 2018; AMA, 2016; Baber et al., 2016; Barbieri, 2019; Endocrine Society, 2019; Davis et al., 2019; NAMS, 2017.

Menopause Society, acknowledged that some patients with special medical needs, (e.g., allergies), may be unable to use certain FDA-approved BHT products, although specific examples of such clinical situations were not provided (NAMS, 2017). Throughout the clinical guidance statements, details regarding the avoidance of select components in FDA-approved BHT products (e.g., due to allergies), were minimal, and the committee could not identify any clinical guidance that outline a therapeutic need for a specific patient population to receive a specific cBHT formulations in lieu of FDA-approved BHT products. Furthermore, based on its review of peer-reviewed literature and clinical guidance statements, the committee was

unable to identify any specific life-threatening medical conditions requiring the patient's use of cBHT preparations.[11]

The Use of cBHT: Specific Medical Needs

As discussed earlier in this report, compounding provides the option to omit components of FDA-approved drug products for patients with specific therapeutic needs that cannot be met by available FDA-approved drug products. Avoiding allergies is one of the most commonly cited historic rationales for compounding (Kelso, 2014; Swerlick and Campbell, 2013). Although there is evidence of allergies to active ingredients in FDA-approved drug products (Roby et al., 2006), the majority of the complaints are related to the inactive ingredients in these drug products (Abrantes et al., 2016).

Recent work characterized the role of inactive ingredients in FDA-approved oral drug products and their potential to trigger allergies in certain subpopulations of patients (Reker et al., 2019). For example, the drug label for Estrace (an FDA-approved estradiol tablet) includes the following warning:

> ESTRACE should not be used in patients with known hypersensitivity to its ingredients. ESTRACE tablets 2 mg, contain FD&C Yellow No. 5 which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity. (NLM, 2018)

Such labels and warnings noting the potential for inducing allergy are not required for compounded preparations, including cBHT. See Chapter 5 for an additional discussion on the inadequate label requirements for cBHT preparations.

Allergies to inactive components in FDA-approved BHT products are commonly expressed rationales for the use of compounded preparations,

[11] It should be noted that medical associations, societies, and other relevant health organizations that issue clinical guidance are often supported, in part, by the pharmaceutical industry. Furthermore, many of the co-authors of the issued guidance conduct medical research that may be funded, in part, by the pharmaceutical industry. All aspects of the pharmaceutical ecosystem (including FDA-approved and compounded drugs) should be extremely mindful of the great responsibility entrusted to them by the public to disclose all conflicts of interest (real and perceived) and to uphold esteemed medical and scientific ethics, values, and standards. After considering the disclosed conflicts of interest for the authors of the clinical guidance reviewed in this report, the study committee had sufficient confidence to allow the guidance to serve as an important piece of evidence used to inform their report conclusions.

in general (NAMS, 2017; Pinkerton, 2020).[12] This stands in direct contrast to the very few published examples of allergic reactions to FDA-approved BHT products and the lack of clinical guidance on this issue. To collect additional insight on this topic, the committee turned to the Endocrine Society for nominations of practicing clinicians who would be able to speak to the medical conditions in which a cBHT preparation would be needed in lieu of FDA-approved treatments. The nominated clinicians, Drs. Cynthia Stuenkel and Nanette Santoro, stated that based on their experience, a small fraction of their patients may show an allergy to a component of FDA-approved BHT products (e.g., peanut oil). The clinicians noted, however, that in most cases there were alternative FDA-approved BHT products that would avoid those conditions (e.g., Bijuva), and given the safety concerns outlined by clinical guidance, only on rare occasions would they prescribe a compounded preparation as an alternative treatment (NASEM, 2019a).

Use of cBHT: Special Patient Populations

In addition to allergies, the committee tried to identify special conditions for which no FDA-approved BHT product exists and special populations requiring specific doses and forms of BHT that could not be treated with FDA-approved medications. Patients with female sexual dysfunction (FSD) and gender dysphoria are two indications for which there are no FDA-approved BHT medications.[13,14] Both are treated off-label with FDA-approved BHT medications (AMA, 2016; Davis et al., 2019).

Female Sexual Dysfunction

Currently, there are no available FDA-approved BHT products to treat the diagnostic classifications of FSD.[15] In addition, after a review of the evidence, the committee could not identify any professional medical organizations with evidence-based clinical guidance that recommend use of cBHT for treating FSD.

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[12] See also Senate Hearing. 110-129—Bioidentical Hormones: Sound Science or Bad Medicine, Hearing for the United States Senate Special Committee on Aging (https://www.govinfo.gov/app/details/CHRG-110shrg37150/CHRG-110shrg37150/summary).

[13] Female sexual dysfunction (FSD) is a complex condition associated with diagnostic classifications including hypoactive sexual desire, sexual arousal disorder, orgasmic disorder, or sexual pain disorder (Lightner, 2002).

[14] A DSM-5 recognized diagnosis that is "a noticeable incongruence between the gender the patient believes they are, and what society perceives them to be" (APA, 2013).

[15] One FDA-approved drug product, Flibanserin, is approved to treat female sexual arousal disorder (FSAD) in premenopausal women, but is a nonhormonal product that includes mixed function serotonin agonist/antagonist (NLM, 2019).

Commonly used treatment options include nonpharmacologic approaches such as education, counseling, or psychotherapy (Clayton et al., 2018; FDA, 2015). For patients seeking hormone therapy options, particularly postmenopausal patients, clinicians often use off-label testosterone treatment regimens—at a dose that is approximately one-tenth of that given to a male—to address symptoms (Clayton et al., 2018).[16] cBHT preparations containing testosterone appear to be an increasingly popular option as a result of the limited number, dosage forms, and dosing options of FDA-approved drug products containing testosterone currently on the market (AMA, 2016; Clayton et al., 2018).

A recent position statement endorsed by several medical societies concluded that the only evidence-based indication for testosterone therapy for women is for the treatment of hypoactive sexual desire disorder (HSSD),[17,18] and that there is insufficient data to support the use of this treatment for any other symptom, clinical condition, or disease prevention (Davis et al., 2019). Regarding use of compounded testosterone therapy, the authors of this position statement concluded that cBHT is not recommended to treat symptoms of HSDD given the lack of evidence for efficacy and safety. The authors noted that an exception can be made if an "authorized equivalent preparation" is not available. In this case, the task force recommends that "the compounding pharmacy should be compliant with purity of active pharmaceutical ingredients and good manufacturing to meet industry standards for quality and safety," and "dosing should be limited to achieving testosterone concentrations in the physiologic premenopausal range" (Davis et al., 2019, p. 4,664).

[16] In addition to testosterone products to treat FSAD, evidence suggests the limited potential for a select few other off-label hormone therapies including, estrogens, ospemifene—a selective estrogen receptor modulator, and dehydroepiandrosterone (DHEA) (AMA, 2016).

[17] This position statement has been endorsed by the International Menopause Society, the Endocrine Society, the European Menopause and Andropause Society, the International Society for Sexual Medicine, the International Society for the Study of Women's Sexual Health, the North American Menopause Society, el Federación Latinoamericana de Sociedades de Climaterio y Menopausia, the Royal College of Obstetricians and Gynaecologists, the International Society of Endocrinology, the Endocrine Society of Australia, and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists.

[18] Prior to the release of the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5), the term *hypoactive sexual desire disorder* (HSDD) was used to describe all disorders pertaining to female sexual dysfunction. After the DSM-5, medical guidance merged the use of HSDD into the singular term *female sexual interest/arousal disorder* (FSIAD or FSAD). However, because HSDD and FSAD are widely considered to be two distinct female sexual dysfunction conditions, the sexual health community has not endorsed or adopted the merging of these terms. Thus, for the purposes of this report, the committee will use the term *female sexual dysfunction*, except when it is necessary to mirror terminology used in the referenced material (Clayton et al., 2018; Davis et al., 2019).

Gender Dysphoria

In recent years, medical researchers and professionals have found hormone therapy to be important and necessary for transgender or transitioning male and female adults and adolescents. Professional medical organizations including the Endocrine Society, the World Professional Association for Transgender Health, and other leaders in transgender health have developed clinical guidance describing off-label use of FDA-approved BHT for this patient population (AMA, 2016; Coleman et al., 2012; Fenway Health, 2015; UCSF Transgender Care, 2016).

Despite the availability of diverse FDA-approved BHT treatment options (e.g., various doses and forms), it is not uncommon for patients with gender dysphoria to be denied coverage for hormone therapy and other treatments under current health care policies (AMA, 2016). Consequently, certain health specialists prescribe cBHT preparations to this patient population (AMA, 2016; Coleman et al., 2012; Fenway Health, 2015; UCSF Transgender Care, 2016). However, the committee could not identify any professional medical organizations with evidence-based clinical guidance that recommend use of cBHT for gender dysphoria, in lieu of off-label use of FDA-approved BHT.

Conclusion 8-1

Evidence-based clinical guidance recommends use of FDA-approved drug products for treatment of menopause and male hypogonadism. Some, but not all, guidelines reviewed acknowledge the potential for limited use of compounded bioidentical hormone therapy in specific medical circumstances, for example, patients with allergies to specific components of FDA-approved hormone therapy, or patients that require a dosage form not currently available as an FDA-approved drug product.

Considerations for Prescribers

There are important professional obligations for licensed physicians who prescribe hormone therapy. Based on the precautionary principle, physicians prescribing FDA-approved BHT and cBHT have a responsibility, where possible, to engage in practice informed by evidence-based clinical guidance. Similar to the guidance outlined by the Federation of

State Medical Boards for prescribing complementary and alternative medicines, providers need to respect patient autonomy—the right of patients to choose—while at the same time educating their patients to ensure that their decision making is based on evidence-based health information and is supported by techniques of shared decision making (Barry and Edgman-Levitan, 2012; Couët et al., 2015; FSMB, 2002; IOM, 2001).

Certain areas of potential liability exist for prescribers of cBHT, including the invalidation of malpractice insurance, personal liability, or possible criminal charges (Sellers and Utian, 2012). For example, at an open session meeting in May 2019, the committee heard testimony from the Tennessee Attorney General's office that described instances in which physicians have lost their medical license and clinics have been closed owing to inappropriate claims regarding the benefits of cBHT without adequate support.[19]

THE USE OF cBHT: PATTERNS AND TRENDS

To identify patterns and trends in the use of cBHT, the committee reviewed available data from published national surveys; peer-reviewed literature; collected testimonies from patients, clinicians,[20] and compounding pharmacists; and data submitted by FDA, the National Association of Boards of Pharmacy (NABP), and the Professional Compounding Centers of America. Insights from this review are presented below.

Insights from Surveys

There are limited peer-reviewed data on historical practices or current trends in the prescription and use of cBHT, and much of what is known comes from small surveys of patients, clinicians, and pharmacists (Constantine et al., 2016; Gass et al., 2015; Pinkerton and Constantine, 2016; Pinkerton and Santoro, 2015; Stuenkel and Manson, 2017). These surveys suggest that between 1.0 and 2.5 million U.S. women age 40 years or older use cBHT, accounting for some 26 million to 33 million prescriptions costing between $1 billion and $2 billion annually, which suggests the use of multiple cBHT prescriptions per individual (Constantine et al., 2016; Gass et al., 2015; Pinkerton and Constantine, 2016; Pinkerton and Santoro, 2015; Stuenkel and Manson, 2017). In a small study of 184

[19] Office of Tennessee Attorney General. 2020. Email from B. Harrell to National Academies staff regarding *State of Tennessee v. HRC Medical Centers, Inc.* legal decision. April 29. Available through the National Academies Public Access File.

[20] Testimony was collected from clinicians who self-identified as having a wide range of professional credentials (e.g., M.D., D.O., registered nurse, nurse practitioner, physician assistant) and specialties (e.g., internal medicine, cardiology, wellness, antiaging medicine, obstetrics and gynecology, family practice, urology, palliative care, pediatrician, emergency medicine).

patients, 77 percent of cBHT users believed it was safer than conventional hormone therapy (Iftikhar et al., 2011). A 2015 NAMS-sponsored online survey of 3,725 women revealed that of the 9 percent currently taking hormone therapy to treat menopausal symptoms, approximately one-third were using cBHT (Gass et al., 2015; see Figure 8-2).

A 2019 survey of compounding pharmacies, which then distributed questionnaires to their patients, produced 494 usable responses (putative response rate of 17.9 percent). From these responses, 50.1 percent of patients indicated their compounded prescriptions were for preparations designed as hormone therapies (McPherson et al., 2019). A survey conducted in Australia between October 2013 and March 2014 distributed questionnaires to 5,850 women identified through the Australian electoral roll. Analyzed results showed that of the 1,491 perimenopausal and postmenopausal women who responded, 1.1 percent used compounded estrogen and/or compounded progesterone and 0.9 percent used dehydroepiandrosterone (DHEA) and/or testosterone (Worsley et al., 2016).

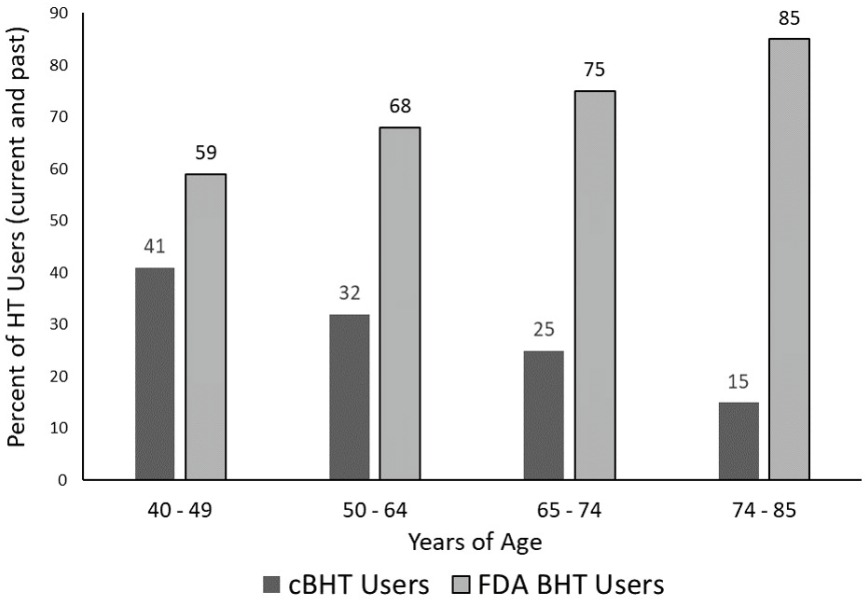


FIGURE 8-2 Age differentials in users of bioidentical hormone therapy: compounded formulations versus FDA-approved drug products. *n* = 3,725; 2015.
NOTE: BHT = bioidentical hormone therapy; cBHT = compounded bioidentical hormone therapy; FDA = U.S. Food and Drug Administration; HT = hormone therapy.
SOURCE: Gass et al., 2015.

It is important to remember there are limited regulatory and statutory requirements for cBHT labeling and package insert information for patients. Consequently, a portion of cBHT patients may not be sufficiently informed as to whether their medication is compounded, FDA-approved, or safe and effective to treat their symptoms. This is an important context to be mindful of when reviewing self-reported survey data on cBHT use.

Insights from the Nurses' Health Study 2

Because the committee was unable to identify publicly available information to conduct an analysis of formulations, frequency, or trends of use of cBHT preparations in the United States, it submitted a request to review unpublished national data from the Nurses' Health Study 2 (NHS2). NHS2 is an ongoing, large, prospective cohort study collecting comprehensive information on the lifestyles and health status of U.S. women in an effort to identify risk factors for major chronic diseases. Since 1976, participants of NHS2 have completed questionnaires every 2 years to update exposures and ascertain outcomes,[21] and every questionnaire cycle has asked women about their use of hormone therapies. In 2015, 87,677 participants were specifically asked for the first time about their use of "bioidentical estrogen," "bioidentical progesterone," and testosterone. In coordination with NHS2 investigators, the committee was able to access data regarding the frequency of use of these bioidentical hormones in this study population (NHS, 2019).

Based on the questionnaire administered in 2015, when the average respondent was age 60 and approximately 10 years postmenopausal, 16 percent of NHS2 participants reported they used some kind of hormone therapy (see Table 8-3). Of those reporting they used hormone therapy, 11 percent reported use of a "bioidentical" product. The most commonly reported bioidentical hormones were a combination of estrogen and progesterone (26 percent), a combination of estrogen, progesterone, and testosterone (25 percent), and testosterone alone (22 percent) (see Table 8-4). The questionnaire did not specifically refer to "compounded" BHT, a common oversight that impedes accurate surveillance of cBHT use.[22,23]

[21] For access to current and past questionnaires, see https://www.nurseshealthstudy.org/participants/questionnaires (accessed January 20, 2019).

[22] In addition, although these data provide some quantitative data as to the frequency of use of bioidentical hormones in the general U.S. population, it may not provide full insight into the potential patient population. The respondents to the NHS2 questionnaire are primarily white, and to what extent similar use patterns exist in nonmedically trained individuals or women of color is not known.

[23] BIJUVA (estradiol and progesterone capsules) is the first only FDA-approved combination BHT product. However, reported use of bioidentical estrogen and progesterone medications does not clarify whether the medication is compounded or FDA approved. Other BHT combinations are likely compounded for use.

TABLE 8-3 Data from the 2015 NHS2 Questionnaire (*n* = 87,677) on Hormone Therapy Use

	Noncurrent Users of HT	Current Users of Conventional HT	Current Users of Bioidentical HT
	n = 73,793	*n* = 12,558	*n* = 1,534
Age, mean (SD)	61 (5)	60 (5)	61 (5)
BMI, Mean (SD)	27.7 (6.4)	27.9 (6.5)	28.3 (6.7)
Age at menopause (SD)	50.0 (4.5)	49.8 (4.5)	49.8 (4.7)
Previous breast cancer (%)	5,102 (6.9%)	1,022 (8.1%)	126 (8.2%)
Postmenopausal (%)	60,900 (82.5%)	10,360 (82.5%)	1,245 (81.2%)

NOTE: BMI = body mass index; HT = hormone therapy; SD = standard deviation.

SOURCE: NHS, 2019.

TABLE 8-4 Frequency of Types of Hormones Among Women Reporting Use of BHT (*n* = 1,534)

Any bioidentical estrogen	248 (16.2)
Any bioidentical progesterone	951 (62.0)
Any Testosterone	335 (21.8)
Bioidentical estrogen only	140 (9.1)
Bioidentical progesterone	121 (7.9)
Bioidentical testosterone only	335 (21.8)
Bioidentical estrogen + testosterone	108 (7.0)
Bioidentical estrogen + progesterone	397 (25.9)
Bioidentical progesterone + testosterone	45 (2.9)
Bioidentical estrogen + progesterone + testosterone	388 (25.3)

SOURCE: NHS, 2019.

cBHT: Types and Amounts of Use

To examine the common types and amounts of cBHT preparations used by patients, the committee gathered descriptive data on dispensed drugs purchased from 503B outsourcing facilities, as well as from information from NABP. In addition, qualitative testimonies by patient, clinician, or pharmacist groups, and responses from a committee stakeholder questionnaire, were reviewed and discussed during committee deliberations.[24]

[24] See Appendix A for additional details regarding the National Academies Committee Stakeholder Questionnaire.

FDA-Submitted Data from 503B Outsourcing Facilities

In May 2019, the committee submitted a data request to FDA for a compiled list of the most commonly dispensed cBHT preparations from registered 503B outsourcing facilities during 2017–2018. These data showed that 503B outsourcing facilities produced 3,777,663 individually packaged compounded hormone products in 2017 and 4,215,899 in 2018, an increase of 11.6 percent. Over this period, testosterone was the most frequently prepared compounded hormone by 503B outsourcing facilities, followed by estradiol, testosterone cypionate, progesterone, and estriol. Estrone, pregnenolone, and DHEA were compounded in small quantities, and estradiol cypionate was not formulated by any of the outsourcing facilities over this 2-year period.[25]

Only three hormones—estradiol, testosterone, and testosterone cypionate—saw an increase in their use in compounded preparations manufactured by outsourcing facilities over the period of 2017–2018 (see Table 8-5). Estriol and progesterone were all used in fewer compounded products coming from 503B facilities in 2018 compared to 2017, with compounding of progesterone-containing products by 503B facilities falling more than 58 percent (see Table 8-5).

The most frequent dosage form depended on the type of hormone contained in the formulation and whether the preparation contained a single ingredient or multiple ingredients. For example, progesterone and testosterone were most commonly compounded as capsules and pellets, respectively. Estradiol was most frequently compounded in pellet form as a stand-alone active product ingredient, but when made into a multi-ingredient product, capsules were the most frequent dosage form produced (see Chapter 5 for more information on the diversity of available cBHT formulations and dosage forms).

Data on cBHT from NABP

In June 2019, the committee submitted a data request to NABP to gather information on the most common formulations dispensed to patients. From its 2016 to 2018 collection of pharmacy inspection application requests, NABP submitted a compiled list of the five most dispensed

[25] FDA 2019 email from G. Cosel to National Academies staff regarding aggregated volume output of products containing ingredients of interest to compounded bioidentical hormone therapy study. May 30, 2020. Available through the National Academies Public Access File. Data were aggregated across all outsourcing facilities in order to keep each outsourcing facilities' production volume confidential. Additional outsourcing facility preparation reports can be found at https://www.fda.gov/drugs/human-drug-compounding/information-outsourcing-facilities (accessed April 13, 2020).

formulations from both 503A compounding pharmacies and 503B outsourcing facilities. In general, the 503A compounding pharmacy data suggested that progesterone in capsules and testosterone in creams were the two most commonly dispensed cBHT preparations, followed by estradiol/estriol and estradiol cream formulations. From NABP's 503B outsourcing facilities data, it appears that progesterone capsules, testosterone pellets, and testosterone cypionate injections were the most commonly dispensed preparations.

Although these data provided a snapshot of the formulations in demand over the last few years, there are substantial limitations. The majority of these reports came from pharmacies that voluntarily approached NABP requesting an inspection (though some inspections were mandated because of state disciplinary action), so they cannot be viewed as representative of the dispensing trends of all 503A compounding pharmacies or 503B outsourcing facilities. In addition, there were instances in which the pharmacists filling out the applications failed to note whether their top hormone therapy medications were FDA approved or compounded, and incompleteness of the submitted data limited their usefulness.[26] Data from 503A compounding pharmacies suggest increased use of progesterone, whereas the data provided by the 503B data outsourcing facilities suggest reduced demand for progesterone. Given the limitations of these data, the committee is unable to reconcile the two submitted data sources (NABP, 2019).

Submitted Testimonials

In addition to reviewing data from clinical guidance, peer-reviewed literature, national surveys, and federal and state databases, the committee also reviewed submitted statements and testimonies from patients, clinicians, researchers, and compounding pharmacists. While these were helpful in verifying the broad spectrum of available cBHT formulations, the information was anecdotal or derived from small or nonrepresentative samples. Additional evidence is needed to provide *quantifiable* and verifiable evidence to examine trends or determine future projections regarding use.

[26] Although the application form specifically asked pharmacists to list their top compounded preparations, there were certain instances where it was not clear whether pharmacists accidently listed FDA-approved drug products. To address this issue in the analysis of the data, if the complete formulation listed was not found in FDA's list of available hormone therapy products, then formulation was counted in the total tally for compounded preparations. If the formulation listed was also found to be available as an FDA-approved drug product, to avoid false positives, this entry was not incorporated into the final data set.

TABLE 8-5 2017–2018 Production Levels of Select Hormones Used in Compounded Preparations by 503B Outsourcing Facilities

	Estriol		Estradiol		Progesterone	
Year of production	2017	2018	2017	2018	2017	2018
Single ingredient formulation	3,822	2,882	619,571	692,879	205,539	82,653
Multi-ingredients (combination) formulation	16,600	13,382	36,839	18,918	15,351	8,912
Total quantity compounded	20,422	16,264	656,410	711,797	220,890	91,565
Percent change in quantity compounded from 2017 to 2018	–20.4		8.4		–58.6	

NOTE: Production levels were measured as individual packages.

SOURCE: NASEM, 2019b.

Additional Concerns

In addition to the limited regulation and oversight of producing and dispensing cBHT medications, there is a lack of standardized data collection and meaningful surveillance of patient use of cBHT preparations. A constantly evolving compounding landscape, including the emergence of large, mail-order compounding pharmacies and recent changes in insurance coverage (McPherson et al., 2019) contribute to the limited data sources. In recent years, payers have drastically reduced their coverage of compounded medications (CMS, 2018; DHA, 2017), but if insurance companies that cover cBHT are tracking prescriptions for compounded medications, these data have not been published widely or analyzed by researchers. Furthermore, no data source exists to capture the use of cBHT by patients who pay out of pocket. Quantifiable data are needed to adequately inform understanding of use and trends, policy decisions related to the clinical utility of cBHT, and other influencing factors, such as financial incentives.[27]

[27] See Chapter 3 for more information on cBHT formulations and conflicts of interest.

Testosterone		Testosterone Propionate		Testosterone Cypionate	
2017	2018	2017	2018	2017	2018
2,691,848	3,165,230	2,330	2,013	139,013	163,765
34,625	52,844	6,197	4,954	5,928	7,467
2,726,473	3,218,074	8,527	6,967	144,941	171,232
18.0		–18.3		18.1	

Conclusion 8-2

The current volume and scope of compounded bioidentical hormone therapy (cBHT) use contrasts with evidence-based clinical guidance issued by professional medical societies and organizations that recommend limited to no use of cBHT preparations for menopausal symptoms.

FACTORS DRIVING THE USE OF cBHT

While there is limited evidence-based support for the use of cBHT to treat menopausal symptoms, the available data suggest millions of patients use thousands of different cBHT formulations every day. Given this fact, the committee deemed it critical in its examination of clinical utility to explore potential factors influencing interest and use of these non-FDA-approved preparations. To address these points, the committee reviewed the potential influence of cBHT marketing; physician practices and perspectives; patient mistrust in the health care industry and commercial pharmaceutical industry; patient interests in the "natural" movement; and prescription costs. Information related to factors influencing use of cBHT came from a few qualitative studies and several hundred testimonials; however, the

committee could not identify any large-scale descriptive surveys of cBHT users to inform its understanding of various influencers.

The Role of Marketing

Media Influence

Published surveys suggest that a substantial number of patients rely on media outlets such as social media, books, Internet marketing, celebrities, and television commercials to educate themselves about cBHT (McPherson et al., 2019; Pinkerton and Santoro, 2015). Much of this information seems to originate from direct-to-consumer marketing by compounding pharmacies and commercial wellness clinics (AMA, 2016; see Table 8-6 for excerpts from select published statements and professional guidance). For example, a 2017 study of 100 websites promoting or offering cBHT services or products identified through a Google search found that nearly

TABLE 8-6 Published Statements and Professional Guidance on the Marketing of Compounded Bioidentical Hormone Therapy

Organization Name	Year	Concerns and Recommendations
American Medical Association	2016	"There have been some ethical and conflict of interest issues associated with commercial wellness clinics and compounding pharmacies that prescribe and dispense CHT. Some compounding pharmacies that sell CHT also market the products to the public by providing listings of their offerings and offer referrals to providers who can prescribe the CHT. Some proprietors of commercial wellness clinics have published peer-reviewed journal articles that have been viewed as misleading and questionable rhetorical approaches may be used to appeal to those lacking scientific literacy, for example, failing to distinguish between 'cutting edge medicine' and 'untested or unproven therapies.'" (AMA, 2016, p. 6)
British Menopause Society (BMS)	2019	"The Advertising Standards Association (ASA) ruled in 2017 against the 'misleading' promotion of cBHRT when a prescribing dermatherapy cosmetic clinic in Stratford upon Avon was reported. This test case led to a ruling being passed that these clinics and prescribers of cBHRT should not claim greater safety and efficacy as there was no evidence from clinical trials for these products. The ASA also advised that there was insufficient evidence that multiple serum and saliva tests could be used to precisely individualize therapy. The public should be cautious of marketing that can give rise to false securities and should avoid purchasing cBHT products over the Internet." (Panay et al., 2019, p. 62)

SOURCES: AMA, 2016; Panay et al., 2019.

half originated from medical clinics (Yuksel et al., 2017). These medical clinics often promoted cBHT preparations as less risky than conventional hormone therapies, with 65 percent of their websites marketing cBHT as having either a lower risk of causing breast cancer risk or even being protective against breast cancer (Yuksel et al., 2017). For further discussion on the use and oversight of marketing, see Chapter 3.

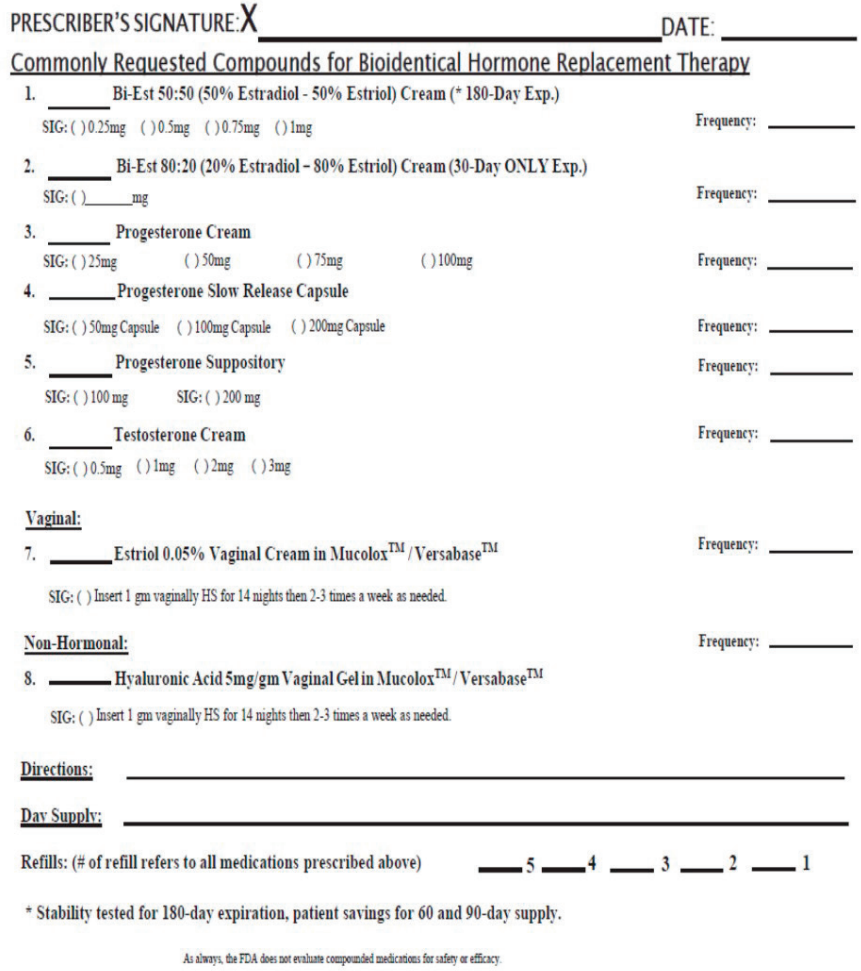
Although there are no specific data to inform conclusions about the effects of celebrity endorsements, there have been a number of highly visible and influential celebrity accounts and endorsements of cBHT over the past 15 years (Pinkerton, 2015). In reviewing the 3,397 patient responses to the committee's stakeholder questionnaire question, "How did you first learn about cBHT products," 202 patients reported online media sources, 94 noted social media discussions, and 93 responded using the "other" option, many noting they got their information from books that were often authored by high-profile celebrities.[28]

Claims of Customization

In contrast to the historic rationales for compounding, advocates of cBHT often promote the view that cBHT medications are superior to FDA-approved BHT because they offer individualized hormone preparations and can provide a wider range of optional doses and dosage forms throughout the course of treatment (AMA, 2016). The prospect of personalized medications and avoiding perceived one-size-fits-all treatments appears to have a substantial appeal to patients (McPherson et al., 2019; Pinkerton and Santoro, 2015; Yuksel et al., 2017). This may be influenced, in part, by popular discourse in both social media and popular press (Marcon et al., 2018).

In contrast to the growing interest in customized and personalized medications, compounders often offer preprinted prescription pads for cBHT with a checklist of popular ingredient combinations, concentrations, and dosage forms (NASEM, 2019c; see Figure 8-3). These are often used as a marketing tool to increase the requests for and sale of cBHT, and they may appeal to certain clinicians by making the compounding prescription process "quick and easy." However, there is no available evidence to suggest the sample menus of formulations, and associated doses and dosage forms, are supported by empirical data related to their safety and efficacy. As a result, there is concern that the goal of treatment customization through the use of compounded medications is being replaced by a list of check boxes without adequate assessment or evaluation of the individual patient's complex needs (NASEM, 2019c).

[28] See Appendix A for additional details regarding the National Academies Committee Stakeholder Questionnaire.



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 Frequency: _____
   SIG: ( ) 100 mg SIG: ( ) 200 mg
6. _____ Testosterone Cream Frequency: _____
   SIG: ( ) 0.5mg ( ) 1mg ( ) 2mg ( ) 3mg

Vaginal:

7. _____ Estriol 0.05% Vaginal Cream in Mucolox™ / Versabase™ Frequency: _____
   SIG: ( ) Insert 1 gm vaginally HS for 14 nights then 2-3 times a week as needed.

Non-Hormonal: Frequency: _____

8. _____ Hyaluronic Acid 5mg/gm Vaginal Gel in Mucolox™ / Versabase™
   SIG: ( ) Insert 1 gm vaginally HS for 14 nights then 2-3 times a week as needed.

Directions: _____

Day Supply: _____

Refills: (# of refill refers to all medications prescribed above) ___5 ___4 ___3 ___2 ___1

* Stability tested for 180-day expiration, patient savings for 60 and 90-day supply.

As always, the FDA does not evaluate compounded medications for safety or efficacy.

FIGURE 8-3 Sample prescription pad from deidentified compounding pharmacy's online advertising for cBHT.
SOURCE: NASEM, 2019c.

Patient Perspectives

The existing data on motivations for use come primarily from a few qualitative studies exploring women's reported reasons for seeking cBHT to treat their menopausal symptoms (Fishman et al., 2015; Thompson et al., 2017). Women taking cBHT seemed to be simultaneously "pulled toward" cBHT and "pushed away" from FDA-approved BHT

by conflicting psychosocial forces (Thompson et al., 2017). Motivations "pulling" patients toward cBHT are beliefs in safer and more "natural" hormone therapy alternatives, beliefs often reinforced by their clinicians. Women were "pushed away" from conventional hormone therapies by an overarching distrust of the medical system, their concerns with conflicts of interest with the pharmaceutical industry, and their fears about the safety of FDA-approved hormone therapy products (Thompson et al., 2017). In addition, some women who turned to cBHT did so out of frustration with clinicians who were unable or unwilling to take their symptoms seriously or provide effective treatments (Fishman et al., 2015).

Beliefs in Safer, More "Natural" Hormone Therapy Alternatives

Patients using cBHT have reported that being "natural" makes cBHT safer than conventional hormone therapy, safe when taken long term, and considered safe for use even for breast cancer survivors (Fishman et al., 2015). Those taking cBHT, however, seemed unaware that there were inadequate safety data supporting cBHT use or that there are bioidentical FDA-approved drug products (Fishman et al., 2015). They also believed the products they were taking were natural rather than synthetic, despite the fact that the hormones used to create certain cBHT medications may be synthesized to become bioidentical. These findings are supported by surveys demonstrating that patients using cBHT hold strong beliefs or report preferences for "natural," customizable medications that they believe have a greater safety profile than FDA-approved hormone therapy products (AMA, 2016; Fishman et al., 2015; Huntley, 2011; Iftikhar et al., 2011; McPherson et al., 2019; Pinkerton and Santoro, 2015; Thompson et al., 2017). These appear to be common misconceptions, and even when these misconceptions are pointed out, some patients continue to believe cBHT preparations are safer than FDA-approved hormone therapies (AMA, 2016; Thompson et al., 2017).

In addition, there are data to suggest patients and even prescribing physicians are uncertain as to whether cBHT preparations are FDA-approved medications (Constantine et al., 2016; Pinkerton and Santoro, 2015). For example, Pinkerton and Santoro (2015) found that out of 801 survey respondents (women ages 45–60), 86 percent did not know whether cBHT was an FDA-approved medication. Misconceptions and inaccuracies by both patients and prescribers regarding the safety and efficacy of compounded preparations are a concern. The inadequate labeling requirements (e.g., unstandardized package inserts for patients, no requirement for boxed warnings) potentially contribute to the lack of informed use.

Physician Input

Consultations with physicians appear to influence patients' interest in and use of cBHT. The committee could identify little about the proportion of clinicians that prescribe cBHT, their specialties, or their rates of prescribing. There are, however, a few small descriptive surveys suggesting that a segment of the medical community considers cBHT preparations an appropriate alternative to FDA-approved therapies.

In a 2019 survey of 494 patients, 78.9 percent said their prescriber was the first person to suggest the option of cBHT (McPherson et al., 2019). In addition, in a nonrepresentative sample of 3,397 cBHT users from the National Academies committee's stakeholder questionnaire, 55.4 percent reported first learning about cBHT from their health care provider.[29] Another small Internet-based survey of 128 physicians reported that, as compared to 56.9 percent of family physicians, only 37.7 percent of obstetricians-gynecologists agreed with the statement, "Patients should be counseled that conventional menopausal hormone therapy is more appropriate than compounded preparations" (Dubaut, 2018). Although there is limited available evidence for the committee to consider, in general, it appears that physicians' beliefs affect their patient's potential use of cBHT.

Mistrust in Health Care Institutions

There are additional influences that "push" patients away from FDA-approved drug products. Over the past four decades, Gallup polling revealed that confidence in almost all U.S. institutions, such as Congress and the news media, has deteriorated, but the most dramatic decline has occurred in "confidence in the medical system," which fell from 80 percent in 1975 to 37 percent in 2015 (Baron and Berinsky, 2019). This apparent public mistrust does not appear to be interpersonal, or directed toward individual health care providers, but rather appears to be institutional, or directed toward medical systems as a whole (Baron and Wolfson, 2019; Pearson and Raeke, 2000).

One factor that may be fueling growing mistrust of health care institutions is the relative deemphasis in developing personal relationships between clinicians and patients that has evolved over the years as the health care system attempts to reduce the costs of care (IOM, 2001). To satisfy the desire for a more personal relationship, some patients show interests in pursuing the services of boutique cBHT compounding pharmacies, all-inclusive wellness centers, or specialized health care providers. In fact, in qualitative studies on menopausal decision making, most interviewed

[29] See Appendix A for additional details regarding the National Academies Committee Stakeholder Questionnaire.

patients who reported receiving cBHT prescriptions described their clinical care experience as superior to their conventional medical care. They were satisfied with the individualized care that they received, time spent at each appointment, and follow-up (Fishman et al., 2015; Thompson et al., 2017).

Mistrust in the Pharmaceutical Industry

Similar to public attitudes toward health care institutions, many people in the United States do not hold drug companies in high regard. A 2012 Harris Poll revealed that only 12 percent of U.S. adults believed pharmaceutical companies to be "generally honest and trustworthy" (Miller, 2013). This mistrust may be rooted in public concerns surrounding drug safety, as was suggested in a 2006 survey (Olsen and Whalen, 2009). The survey included 1,726 respondents and evaluated the U.S. public's perception of FDA, the pharmaceutical industry, and Congress (Olsen and Whalen, 2009). Overall, 96 percent of respondents indicated having some degree of concern about prescription drug adverse reactions, even when these drugs are taken as prescribed. Moreover, 42 percent of respondents said that they were either "somewhat distrusting" or "strongly distrusting" of pharmaceutical companies, in general.

Cost Considerations for cBHT

The overall cost of hormone therapy for managing menopause-related vasomotor symptoms are substantial and commonly include routine physician consultations, laboratory testing, and management of adverse events (Utian, 2005). According to a 2016 survey, 26 to 33 million cBHT prescriptions were filled annually with total sales estimated at $1.3 billion to $1.6 billion (Pinkerton and Constantine, 2016). With annual costs of conventional FDA-approved hormone therapies ranging from $430 to $830, patients experiencing menopausal symptoms may seek alternative treatments, including cBHT, that are often marketed as safer and less expensive (PCCA, 2019; Williams-Frame and Carpenter, 2009).[30]

Although recent studies have highlighted the increasing cost of compounded medications, no studies have specifically examined the cost of cBHTs. Based on results from a national survey, McPherson et al. reported that overall out-of-pocket costs for cBHTs may be higher than those of noncompounded prescriptions. The average out-of-pocket cost reported for cBHTs was $88 in a 2017 survey, whereas the average price of FDA-approved postmenopausal hormone therapy prescriptions was $49

[30] A 2019 PCCA national survey of 14 within-network pharmacies, concluded that the median sales price of select cBHT was lower than the median sales prices of select FDA-approved BHT products (available through the National Academies Public Access File).

(McPherson et al., 2019). As an illustrative example of costs, in a testimony, submitted to the committee by a prescriber of cBHT, the cost of topical cBHT preparations (Bi-Est/Tri-Est, progesterone, testosterone, and DHEA) was estimated to range from $40 to $60 per prescription per month depending on the compounding pharmacy, liquid base used, and dispensing method (NASEM, 2019d). The total cost per patient can amount to $80 to $120 per month initially; however, total cost may increase to $160 to $220 per month by 3 years into menopause. Additional testing associated with treatment can cost $285 to $360 for hormone testing and $180 out-of-pocket for ancillary testing (mammography, bone density, and blood tests covered by insurance). Annual consultation and office visit fees can be estimated from $800 to $3,000 (NASEM, 2019d).

Overall, true cost comparisons between cBHT and FDA-approved versions are complicated, given that an individual patient's out-of-pocket costs will vary greatly based on his or her insurance status and other medication use. With the volume of prescribed cBHTs increasing, additional studies investigating the cost and the relationship between cost and use of cBHT and FDA-approved treatments for menopause- and male hypogonadism-related symptoms are needed (Pinkerton and Constantine, 2016). In the meantime, patient preference for costs should be discussed in the context of safety and effectiveness; however, these cost considerations cannot supersede those related to the medication's safety and effectiveness.

Conclusion 8-3

Drivers of patient interest and use of compounded bioidentical hormone therapy (cBHT) may include, but are not limited to, unsubstantiated marketing claims of superior safety and effectiveness, boutique patient experience, financial costs, and the appeal of "natural" hormones and/or dosage forms. In the absence of safety and effectiveness data of cBHT, aspects of patient preference should not be the sole driver for use.

Conclusion 8-4

There is a lack of easily accessible, accurate, and understandable information about compounded bioidentical hormone therapy (cBHT), leading to widespread misunderstanding of the regulation, safety, and effectiveness of cBHT preparations. This lack of information may impact patient and provider risk–benefit considerations.

CONCLUDING STATEMENTS

In summary, after considering the paucity of evidence, including, but not limited to peer-reviewed literature, clinical guidance issued by professional medical organizations, and oral and written public statements from patients, prescribers, and pharmacists, the committee has concerns regarding the current volume and scope of use of cBHT. Reviewed clinical guidance indicated there may be a small population of patients with a therapeutic need for cBHT, including those with an allergy or intolerance to an ingredient within an FDA-approved BHT product. However, data suggest there may be millions of patients using cBHT, implying cBHT preparations are being prescribed for reasons outside of recognized therapeutic need. As noted in a 2018 National Academies report, research results that lack clear clinical utility may still have personal meaning to a patient or participant. Nevertheless, existing frameworks tend to prioritize clinical utility over personal meaning or preference when assessing the value of prescribing a particular drug (NASEM, 2018).

Throughout the course of this study, prescribers, patients, and advocates of cBHT submitted written statements and public testimony sharing their experiences with cBHT. It is clear from these communications that many clinicians, compounding pharmacists, and patients using cBHT hold minimum, if any, concerns regarding the medications' safety and effectiveness. The evidence suggests that confounding factors, including unsubstantiated marketing claims, general misinformation, a mistrust of the pharmaceutical and health care industries, and cost may influence patient perspectives on overall clinical utility of cBHT. This implies that there are opportunities for new or expanded continuing education efforts for clinicians, as well as science communication and health literacy initiatives for patients regarding the effectiveness and safety of both FDA-approved BHT and cBHT.

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9

Clinical Utility and Recommendations

This committee was charged with summarizing findings and making recommendations with respect to the *clinical utility* of treating patients with compounded bioidentical hormone therapy (cBHT) preparations—including a review of whether the available evidence of their safety and effectiveness supports use of cBHT preparations to treat patients, and whether there are special populations that might need cBHT preparations, in lieu of available U.S. Food and Drug Administration (FDA)-approved products. In this final chapter of the report, the committee summarizes its key findings and conclusions regarding the clinical utility of cBHT preparations, and notes the critical importance of evidence-based clinical guidance and its use by clinicians to support positive health outcomes for patients.

WHAT DOES "CLINICAL UTILITY" MEAN?

As discussed in Chapter 1 of this report, *clinical utility* is a multidimensional, context-dependent term for which no standardized definition exists. Given this, the committee turned to the literature, position statements and guidance issued by professional medical societies and associations, stakeholder testimony, and submitted resources to gain a better understanding of the potential components of clinical utility and the varied contexts in which to consider the use of the term.

Literature references to clinical utility point to a range of clinical- and scientific-based examples that reflect the various components of the term (e.g., Ahn et al., 2019; Bagheri et al., 2019; Canter et al., 2019; Challener

et al., 2019; First, 2019; Grosse, 2006; Ishikawa et al., 2019; Johansen Taber, 2019; Lee, 2019; Lesko, 2010; McCormack, 2015; Michel, 2019; Miller, 2019; NASEM, 2018; Oh et al., 2019; Osumi, 2019; Setlur, 2019; Soh, 2019; Teutsch et al., 2009; Vlahos, 2019; Zago et al., 2018). Based on insights from the literature, an entity that is said to have *clinical utility* has been described as being able to:

- Optimize treatment and short- and long-term health outcomes
- Affect diagnostic testing processes
- Assist with patients' decision making
- Offer psychological benefits to the patient, including improved health literacy
- Improve society

Furthermore, the evidence describing the components of clinical utility is not confined to randomized controlled trials; rather, it takes into account a broad range of factors (e.g., Lesko 2010; Miller, 2019). These components include:

1. The current standard of care
2. The care setting
3. Costs of care and tests
4. The nature of what is being evaluated for clinical utility

In its review of clinical utility, however, the committee is aware that these examples were not necessarily all-inclusive and that the term *clinical utility* may potentially encompass additional components not necessarily reflected in existing definitions. In consideration of this guidance, for the purpose of this report, the committee has defined clinical utility as a multidimensional construct that reflects evidence about safety, effectiveness, and therapeutic need.[1] Patient preference is also a component of clinical utility, and it reflects patients' individual decision making based on variable acceptance of benefits and risks. In its approach to examine the clinical utility of prescribing cBHT to patients, the committee systematically reviewed the available evidence relevant to each component of this definition.

[1] In the context of this report, *therapeutic need* relates to the treatment of menopausal and male hypogonadism symptoms.

THE CLINICAL UTILITY OF cBHT AND RELATED CONSIDERATIONS

Table 9-1 provides an overview of the committee's major conclusions related to the clinical utility of cBHT. In summary, evidence suggests the current use of cBHT exceeds the small potential therapeutic need for cBHT. The committee concluded there are insufficient data to support that cBHT preparations are as safe as or safer than FDA-approved hormone therapy, and that inadequate oversight and reporting of adverse events are a public health concern. Similarly, the committee concluded there are insufficient data to support that cBHT preparations are as effective as or more effective than FDA-approved hormone therapy. Therefore, in consideration of clinical utility, current volume use of cBHT appears to reflect patient and prescriber preference for cBHT. Marketed claims, as well as celebrity endorsements, likely influence the use of, or patient preference for, cBHT. In addition, collected testimonies suggest there is widespread misunderstanding of the regulation, safety, and effectiveness of cBHT, and that these gaps in knowledge undermine accurate consideration of risks and benefits of cBHT use. Taken together, the evidence suggests that factors, including marketing claims, general misinformation, a mistrust of the pharmaceutical and health care industries, and cost may influence patient perspectives on overall clinical utility of cBHT.

Through anecdotal testimonies and a few qualitative studies, the committee was made aware of the strong preferences for individualized treatment among certain individuals who use cBHT; however, safety and effectiveness are foundational to assessing its overall clinical utility. Given the paucity of data on the safety and effectiveness of cBHT, the committee made the following conclusion:

Conclusion 9-1

There is insufficient evidence to support the overall clinical utility of compounded bioidentical hormone therapy as treatment for menopause and male hypogonadism symptoms.

However, within the body of evidence reviewed, there are potentially a few specific medical circumstances for which there may be clinical utility of cBHT, such as patients who have an allergy to specific ingredients in an FDA-approved drug product, or patients that require a dosage form not currently available as an FDA-approved drug product. Should further data

TABLE 9-1 Summary of Key Conclusions Related to the Clinical Utility of cBHT Preparations

Components of Clinical Utility	Key Conclusions from the Report
Safety and effectiveness	• Strengthening federal and state regulatory oversight, as well as requirements for transparency and disclosure of conflicts of interest, could contribute to safer, more effective use of compounded preparations, including compounded bioidentical hormone therapy. (Chapter 3) • Currently, cBHT preparations are not adequately labeled. Missing information includes, but is not limited to, a description of the preparation's instructions for use, contraindications, potential adverse effects, boxed warnings, and the identity of the person and company responsible for a compounded preparation's quality and safety. This lack of information undermines safe and effective use by patients and prescribers. (Chapter 5) • cBHT pellet formulations may be difficult to compound given the complexity of drug delivery mechanism, lack of required bioavailability testing, insufficient guidance for compounders, and the need for specialized equipment. Given the broad scope of available cBHT pellet formations marketed for use, and questions regarding difficulty in compounding, there are concerns for safety and effectiveness. (Chapter 5) • The paucity of reliable pharmacokinetic and bioavailability data for cBHT preparations as compared to FDA-approved drug products, compromises the ability to evaluate the safety, efficacy, and product-to-product variability of cBHT preparations. (Chapter 6) • There is a dearth of high-quality evidence—data from studies that would meet FDA's requirements for granting regulatory approval to a drug product—available to establish whether cBHT preparations are safe and effective for their prescribed uses. (Chapter 7) • Well-designed and properly controlled clinical trials are needed to provide reliable evidence about the safety and effectiveness of cBHT preparations. (Chapter 7) • The majority of marketing claims about the safety and effectiveness of cBHT preparations, whether in absolute terms or in comparison to FDA-approved BHT, are not supported by evidence from well-designed, properly controlled studies. (Chapter 7) • There are concerns with the voluntary and incomplete nature of adverse events reporting for compounded preparations. The lack of an easily accessible safety database limits assessment of the frequency, type, and severity of adverse events related to the use of cBHT. Improved monitoring of adverse events is required to characterize the safety of these compounded preparations. (Chapter 7)

TABLE 9-1 Continued

Components of Clinical Utility	Key Conclusions from the Report
Therapeutic need	• Evidence-based clinical guidance recommends use of FDA-approved drug products for treatment of menopause and male hypogonadism. Some, but not all, guidelines reviewed acknowledge the potential for limited use of cBHT in specific medical circumstances, for example, patients with allergies to specific components of FDA-approved hormone therapy, or patients that require a dosage form not currently available as an FDA-approved drug product. (Chapter 8) • The current volume and scope of cBHT use contrasts with evidence-based clinical guidance issued by professional medical societies and organizations that recommend limited to no use of cBHT preparations for menopausal symptoms. (Chapter 8)
Patient preference	• Drivers of patient interest and use of cBHT may include, but are not limited to, unsubstantiated marketing claims of superior safety and effectiveness, boutique patient experience, financial costs, and the appeal of "natural" hormones and/or dosage forms. In the absence of safety and effectiveness data of cBHT, aspects of patient preference should not be the sole driver for use. (Chapter 8) • There is a lack of easily accessible, accurate, and understandable information about cBHT, leading to widespread misunderstanding of the regulation, safety, and effectiveness of cBHT preparations. This lack of information may impact patient and provider risk–benefit considerations. (Chapter 8)

from well-controlled clinical trials become available, such evidence could be evaluated and the clinical utility of cBHT preparations could be reassessed.

Considerations for Health Care Practitioners and Clinicians

Acknowledging, on the one hand, the substantial interest in and use of cBHT, and on the other, a lack of evidence to support the clinical utility of cBHT, the committee recognizes that there exist important professional obligations for stakeholders (i.e., physicians who prescribe and pharmacists who compound and fill these prescriptions) to uphold. These obligations include respecting patient autonomy—meaning the right of patients to choose—while at the same time ensuring that patients' decision making is informed by the best available evidence and supported with shared decision making.

Based on the precautionary principle, physicians who prescribe hormone therapy, both FDA-approved drug products and compounded preparations, have a duty to engage in practice informed by evidence-based clinical guidelines and to educate patients to ensure their decision making is

based on evidence-based health information and is supported by techniques of shared decision making. Health literacy and its reliance on best available evidence is foundational to autonomous patient decision making, and patients must have ready access to the best available evidence that is easy to understand and use as they weigh the risks and benefits of therapeutic options. Considering these obligations, concerns arise from areas of potential liability for prescribers of cBHT, which may include the invalidation of malpractice insurance, personal liability, or possible criminal charges

Pharmacists and other qualified compounders have a professional obligation to follow standards issued by the United States Pharmacopeia to ensure safe preparation and dispensing of all compounded medications in order to minimize safety concerns. They also have an obligation to provide clear directions for use, disclose a clear rationale for the inclusion of each ingredient used in the medication, and include evidence-based information about the medication's potential adverse effects.

RECOMMENDATIONS

There is a dearth of evidence to support many of the marketed claims for the clinical utility of cBHT as a treatment for menopausal and male hypogonadism symptoms. Based on its examination of its clinical utility, the committee recommends restricted use of cBHT, assessments of their difficulty to compound, and additional education, oversight, and research.

Recommendation 1: Restrict the use of compounded bioidentical hormone therapy (cBHT) preparations.
Prescribers should restrict the use of cBHT preparations to the following: documented allergy to an active pharmaceutical ingredient or excipient of U.S. Food and Drug Administration (FDA)-approved drug product, or a documented requirement for a different dosage form. Patient preference alone should not determine the use of cBHT preparations.

In general, the potency of cBHT doses should not exceed those of FDA-approved hormone therapy products because of potential safety concerns. Any use of cBHT, including therapy for gender dysphoria, should align with established clinical guidance and require documentation of shared decision making and rigorous monitoring for long-term risks.

Prescribers and compounding pharmacists should clearly explain the limited evidence-based information about the safety and effectiveness of cBHT preparations. They should inform patients that compounded preparations are not FDA approved.

Recommendation 2: Review select bioidentical hormone therapies and dosage forms as candidates for the U.S Food and Drug Administration (FDA) Difficult to Compound List.
The Pharmacy Compounding Advisory Committee should review the following bioidentical hormone therapies as candidates for FDA's Difficult to Compound List: estradiol, estrone, estradiol cypionate, estriol, dehydroepiandrosterone, pregnenolone, progesterone, testosterone, testosterone cypionate, and testosterone propionate. These candidates have safety and efficacy concerns related to the lack of bioavailability data and product-to-product variability as a result of drug formulation differences, stability, and quality control.

The Pharmacy Compounding Advisory Committee should consider all compounded bioidentical hormone therapy preparations formulated in pellet dosage form as candidates for FDA's Difficult to Compound List.

Recommendation 3: Improve education for prescribers and pharmacists who market, prescribe, compound, and dispense compounded bioidentical hormone therapy (cBHT) preparations.
To ensure the appropriate clinical use of cBHT, the committee recommends the following for prescribers:

- State medical boards, the Federation of State Medical Boards, and medical professional societies and associations (e.g., American Medical Association [AMA], Endocrine Society, North American Menopause Society) should advocate for a state-level certification for individuals who are seeking to begin or continue to prescribe cBHT. Formal clinical education should be offered in parallel to continuing medical education courses.
- Nonprofit professional societies and organizations within the medical sectors (e.g., AMA) should expand and promote evidence-based guidelines and best practices for clinicians who prescribe or compound cBHT preparations. These guidelines should include not only evidence-based conclusions on the potential benefits and risks, but also practical steps of when to consider cBHT in lieu of U.S. Food and Drug Administration (FDA)-approved products, which potential formulations should be considered, and the contraindications associated with the treatment.

To ensure the appropriate clinical use of cBHT, the committee recommends the following for prescribers and pharmacists:

- State boards of pharmacies, National Association of Boards of Pharmacy, Pharmacy Compounding Accreditation Board, local and regional schools of pharmacies, and nonprofit professional societies and organizations within the medical and pharmaceutical sectors with a particular focus in epidemiology and women's health (e.g., American Association of Colleges of Pharmacy, AMA, Endocrine Society, North American Menopause Society) should develop pathways to support and incentivize the attainment of more in-depth training on complex compounding of hormone preparations. These courses should do the following:
  - Be conducted by schools of pharmacy or nonprofit professional societies and organizations within the medical and pharmaceutical sectors.
  - Include a review of the compounding process, including complexities of formulation science.
  - Examine the current peer-reviewed, evidence-based conclusions on the safety and effectiveness of commonly prescribed cBHT preparations.
  - Review the potential risks and reported adverse effects associated with the use of cBHT and FDA-approved products with the same active ingredients.
  - Describe potential conflicts of interest that exist within the prescribing, compounding, and treatment sectors of pharmaceutics.
- Additional continuing medical education courses hosted by for-profit organizations should not substitute for this training.

Recommendation 4: Additional federal and state-level oversight should be implemented to better address public health and clinical concerns regarding the safety and effectiveness of compounded bioidentical hormone therapy (cBHT).

The National Association of Boards of Pharmacy (NABP) and state boards of pharmacy should expand and improve their oversight and review of 503A compounding pharmacies to ensure that adequate quality standards are maintained and documented for every cBHT preparation dispensed. This increased oversight should include the following:

- All 503A compounding pharmacies should provide a standardized insert for dispensed cBHT preparations. The insert should:
  - Include a detailed description of the preparation's formulation, including all active pharmaceutical ingredients and the excipient(s) used, and use of the established name of the drug.
  - Clearly note that the preparation has not been U.S. Food and Drug Administration (FDA) approved for use and that

rigorous bioavailability data, such as that available on FDA-approved products, are not available.
    - Include indications and guidance for use (administration), dosage strength and form, statement of compliance to current good manufacturing practices or United States Pharmacopeia (USP) standards, beyond use date, contraindications, side effects, caution for potential adverse effects, and instructions on how to report adverse events.
    - Include information on the person responsible for the quality and safety of the dispensed cBHT preparation, such as the establishment's supervising pharmacist or other designated individual, and the name and contact information for the pharmacy.
- All cBHT preparations dispensed from 503A compounding pharmacies should include boxed warnings for potential adverse effects for compounded prescriptions that include estrogens (estradiol, estriol, estrone) and androgens (testosterone), like those used in FDA-approved drug products with boxed warnings to educate the user about potential health risks.
- All 503A compounding pharmacies should increase their surveillance capacity by monitoring, recording, and annually reporting the types, formulations, payer, and dispensing rates of cBHT preparations. Data on the volume and types of cBHT dispensed should be submitted annually to a central repository within NABP and made available for public access.
- All 503A compounding pharmacies should be required to monitor and report all adverse events of cBHT preparations to state boards of pharmacy and simultaneously to MedWatch and the FDA Adverse Event Reporting System. Annual adverse event reports for nonsevere and non-life-threatening events should also be submitted. These reports should include information on the frequency, type, and severity of adverse events related to the use of cBHT.
- All states should uniformly and immediately adopt USP <795> and <797> standards to ensure the quality of dispensed sterile and nonsterile cBHT preparations. USP <795> and <797> should be considered minimum standards, and regulators should apply additional standards where needed to reduce patient risk.

FDA should continue to incorporate public health considerations into its regulation of the manufacturing, testing, and dispensing of cBHT by 503B outsourcing facilities. These considerations should include:

- Expand the requirement for 503B outsourcing facilities to provide information on the bioavailability and effectiveness of common

cBHT preparations (e.g., Bi-est, Tri-est, all sterile preparations including pellets), in addition to their current focus on quality, purity, and sterility.

- All 503B outsourcing facilities should use a standardized insert for dispensed cBHT preparations. In addition to the current requirements, the insert should include:
  - A detailed description of the preparation's formulation, including all active pharmaceutical ingredients and inactive ingredients (e.g., excipients) used.
  - Clearly note that the preparation has not been FDA approved for use, and that rigorous bioavailability data, such as that available on FDA-approved products, are not available.
  - Include indications and guidance for use (administration), dosage strength and form, statement of compliance to current good manufacturing practices or USP standards, beyond use date, contraindications, side effects, caution for potential adverse effects, and instructions on how to report adverse events.
- All cBHT supplied by 503B outsourcing facilities should include boxed warnings for potential adverse effects for compounded prescriptions that include estrogens (estradiol, estriol, estrone) and androgens (testosterone), like those used in FDA-approved drug products with boxed warnings to educate the user about potential health risks.
- Modify the standard MedWatch form to adequately collect and track adverse events data related to cBHT use, including but not limited to:
  - All active pharmaceutical ingredients and excipients in the cBHT formulation.
  - Potential drug–drug interactions.

Recommendation 5: Collect and disclose conflicts of interest. Prescribers and compounders of compounded bioidentical hormone therapy (cBHT) may have conflicts of interest arising from financial relationships (e.g., ownership or investment interests held in specific cBHT formulations or companies), and such conflicts should be transparent, publically available, and disclosed to patients at the point of care. In addition, state licensing boards should collect and archive information on such financial relationships in a publicly accessible repository.

Recommendation 6: Strengthen and expand the evidence base on the safety, effectiveness, and use of compounded bioidentical hormone therapy (cBHT) preparations.

As the field of personalized medicine continues to expand, interest in compounded medication is likely to grow. Ensuring the safe and appropriate dosing of cBHT formulations requires the evaluation of the bioavailability of all active ingredients included in the preparation.

To develop a comprehensive evidence base on the potential health benefits and risks of specific cBHT preparations, public agencies (e.g., National Institutes of Health) and philanthropic funding agencies should establish, provide, or increase funding for clinical, epidemiologic, and health services research to address gaps in the evidence base.

Other stakeholders, including the U.S. Food and Drug Administration (FDA), the United States Pharmacopeia, 503A compounding pharmacies and 503B outsourcing facilities, state medical boards, state boards of pharmacy, nonprofit professional societies and organizations within the medical and pharmaceutical sectors, pharmaceutical industries, and clinical and public health research groups should advocate for and support these research initiatives. Stakeholders should also develop a strategic plan to support precompetitive research projects and activities.

Prioritized research objectives should include, but not be limited to, the following:

- Data collection and surveillance.
  - Accurate and consistent collection of adverse event data for each cBHT preparation, by formulation and compounder.
  - Accurate determination of volume, scope, and financial costs of prescribed cBHT preparations in the United States.
- Clinical research on safety and efficacy.
  - Conduct additional well-controlled trials (with or without active comparators) for commonly prescribed cBHT preparations and dosage forms, including formulations that include estrone, estradiol, estriol, progesterone, or testosterone, to examine effects on safety and symptoms associated with perimenopause and menopause.
  - Generate bioavailability data for all active ingredients in the most commonly prescribed cBHT preparations to inform safe and effective dosing practices. Studies that include FDA-approved hormone therapy products with comparable active ingredients and dosage forms may help to inform clinical practice.
  - Develop observational studies of genetic and lifestyle variation (smoking, alcohol, diet) in cBHT responses, including adverse events.

All clinical trials or observational studies related to the safety, effectiveness, and use of cBHT should register with and be approved by an appropriate institutional review board, as well as obtain informed consent from all patients and study participants.

Appendix A

Study Approach

Responding to a request by the U.S. Food and Drug Administration (FDA), the National Academies of Sciences, Engineering, and Medicine's Committee on the Clinical Utility of Treating Patients with Compounded Bioidentical Hormone Replacement Therapy was charged with reviewing use patterns of compounded bioidentical hormone therapy (cBHT), the physiochemical properties of cBHT, and the available evidence on the safety and effectiveness of cBHT preparations.

COMMITTEE EXPERTISE

The National Academies appointed a 12-member committee of experts to address objectives in the Statement of Task. The resulting committee included experts in a variety of disciplines and fields, including drug research and development, pharmacology, toxicology, endocrinology, epidemiology, health literacy, pharmaceutical compounding and manufacturing, health risk mitigation, and health policy.

MEETINGS AND INFORMATION-GATHERING ACTIVITIES

The committee deliberated from March 2019 to April 2020, during the course of which it held five in-person meetings (March, May, June, August, and November) and four virtual meetings (one in September, two in January, and one in April). The March, May, June, and November meetings included portions open to the public. One of the January virtual

meetings was open in its entirety. All other meetings were closed to support the committee's private deliberations.

In the open session meetings, the committee heard presentations from invited content experts on a wide variety of topics related to the committee's charge. These open-session meetings also included periods of public comment, to provide an additional opportunity to present the committee with relevant information. The agendas for the five open-session meetings are presented here.

First Committee Meeting

Open Session Agenda

Tuesday, March 5, 2019
National Academies Keck Center
500 Fifth Street, NW, Washington, DC 20001

Part I
Sponsor Briefing: Discussion of the Committee's Charge

1:15 p.m. **Welcome and Introductions**
JEROME (JERRY) STRAUSS III
Committee Chair

1:20 p.m. **Sponsor Perspective on Charge to the Committee**
RUEY JU, *Study Sponsor*
U.S. Food and Drug Administration

LESLEY FURLONG, *Study Sponsor*
U.S. Food and Drug Administration

2:00 p.m. **Discussion with Committee**

2:45 p.m. **BREAK**

Part II
Additional Context for the Study

3:00 p.m. **Key Stakeholder Perspectives**
BARBARA EXUM, *Director*
Center for Compounding Practice and Research
Virginia Commonwealth University

TIMOTHY MCPHERSON, *Professor* [REMOTE]
Department of Pharmaceutical Sciences
Southern Illinois University, Edwardsville

NESE YUKSEL, *Professor*
Faculty of Pharmacy and Pharmaceutical Sciences
University of Alberta

4:00 p.m. **Discussion with Committee**

4:45 p.m. **Public Comments**

5:00 p.m. **ADJOURN**

Second Committee Meeting

Open Session Workshop Agenda

Monday, May 6, 2019
National Academies Keck Center
500 Fifth Street, NW, Washington, DC 20001

9:00 a.m. **Introductions**
LEIGH MILES JACKSON, *Study Director*
Board on Health Sciences Policy
Health and Medicine Division

DONALD MATTISON, M.D.
Committee Chair

RUTH PARKER, M.D.
Committee Vice Chair

Session I
Context for the Current Study

9:10 a.m. **Overview Session**
CYNTHIA STUENKEL, M.D.
University of California, San Diego

BRANT HARRELL
Office of Tennessee Attorney General

SARA ROTHAMN
U.S. Food and Drug Administration

9:55 a.m. **Discussion and Q&A**

Session II
Consumer Engagement, Education, and Medical Care

10:40 a.m. **Perspectives from Consumers, Educators, and Medical Care Providers**

Consumer Education Perspectives

PHYLLIS GREENBERGER, M.S.W.
Healthy Women

CINDY PEARSON, M.D. [REMOTE]
National Women's Health Network

LYN HOGREFE [REMOTE]
Happy Hormone Cottage

Provider Perspectives

NANETTE SANTORO, M.D. [REMOTE]
University of Colorado Denver

ADRIAN SANDRA DOBS, M.D., M.H.S.
Johns Hopkins University School of Medicine

WANDA DYSON, M.D.
Change for Life Wellness & Aesthetics

DAVED ROSENSWEET, M.D.
The Menopause Method

12:40 p.m. **LUNCH BREAK**

Session III
Pharmaceutical Sciences and Compounding Panel

1:45 p.m. **Perspectives from Compounding Pharmacists**

A. J. DAY, PHARM.D., R.PH. [REMOTE]
Professional Compounding Centers of America

GUS BASSANI, PHARM.D.
Professional Compounding Centers of America

JIM HRNCIR, R.PH.
Las Colinas Pharmacy

LOYD ALLEN, JR., PH.D., R.PH. [REMOTE]
International Journal of Pharmaceutical Compounding

3:15 p.m. **Discussion with Committee**

4:00 p.m. **Public Comments**

4:15 p.m. **ADJOURN**

Third Committee Meeting

Open Session Agenda

Thursday, June 27, 2019
National Academies Keck Center
500 Fifth Street, NW, Washington, DC 20001

12:45 p.m. **Welcome and Introductions**
DONALD MATTISON, M.D.
Committee Chair

RUTH PARKER, M.D.
Committee Vice Chair

12:50 p.m. **Presentations from Invited Speakers**
LOYD ALLEN, JR., PH.D., R.PH.
International Journal of Pharmaceutical Compounding

JANE AXELRAD, J.D.
Axelrad Solutions LLC

REBECCA GLASER, M.D.
Millennium Wellness Center

2:45 p.m. **Public Comments**

3:00 p.m. **Adjourn**

Sixth Committee Meeting

Open Session Agenda

Tuesday, November 12, 2019
National Academies Keck Center
500 Fifth Street, NW, Washington, DC 20001

12:45 p.m. **Doors Open**

1:00 p.m. **Introductions**
Leigh Miles Jackson, *Study Director*
Board on Health Sciences Policy
Health and Medicine Division

Donald Mattison, M.D.
Committee Chair

Ruth Parker, M.D.
Committee Vice Chair

1:05 p.m. **Perspectives from Professional Associations and Organizations**
Thomas Menighan, B.S.Pharm., M.BA., Sc.D. (Hon), FAPhA
Executive Vice President and Chief Executive Officer
American Pharmacists Association

Ronna B. Hauser, Pharm.D.
Vice President
Policy & Government Affairs Operations
National Community Pharmacist Association

1:30 p.m. **Q&A and Discussion (moderated by committee members)**

1:45 p.m. **Perspectives from Providers**
Gary S. Donovitz, M.D., FACOG
Founder
BioTE Medical, LLC

Pamela Smith, M.D., M.P.H., M.S.
Founder and Director
Center for Personalized Medicine

2:15 p.m. **Q&A and Discussion (moderated by committee members)**

2:45 p.m. **BREAK**

3:00 p.m. **Perspectives from Compounding Pharmacists**
PETER KOSHLAND, PHARM.D.
Chief Executive Officer
Koshland Pharmacy

GINA BESTEMAN, R.PH.
Director
Compounding and Dispensing
Women's International Pharmacy

3:30 p.m. **Q&A and Discussion (moderated by committee members)**

4:00 p.m. **Public Comments**

4:30 p.m. **ADJOURN**

Seventh Committee Meeting

Open Session Agenda

Tuesday, January 14, 2019

12:00 p.m. **Introductions**
LEIGH MILES JACKSON, PH.D., *Study Director*
Board on Health Sciences Policy
Health and Medicine Division

DONALD MATTISON, M.D.
Committee Chair

RUTH PARKER, M.D.
Committee Vice Chair

12:05 p.m. **Perspectives from Invited Speakers**
RACHEL PONTIKES, J.D.
Partner
Reed Smith LLP

Angela DeRosa, D.O., M.B.A.
Medical Director
Belmar Pharmacy & Belmar Select Outsourcing

Doug Cammann, R.Ph.
Vice President
Operations
AnazaoHealth Corporation

Donald Prentiss
President
Operations
Carie Boyd's Prescription Shop

Thomas C. Kupiec, Ph.D.
President and Chief Executive Officer
ARL BioPharma, Inc., DNA Solutions, Inc.,
The Kupiec Group, LLC

1:20 p.m. **Q&A and Discussion (moderated by committee members)**

1:40 p.m. **Public Comments**

2:00 p.m. **ADJOURN**

RESOURCES SUBMITTED BY STAKEHOLDERS

Recognizing the limited information available addressing the use, safety, effectiveness, and patient perspectives of cBHT, the committee also made concerted efforts to collect and review relevant anecdotal, survey, and (when possible) quantitative data from national stakeholders to supplement their research efforts. For example, relevant data were submitted by stakeholders, including FDA, Professional Compounding Centers of America, National Association of Boards of Pharmacy, Massachusetts Board of Registration in Pharmacy, Office of Tennessee Attorney General, National Women's Health Network, representatives of 503A compounding pharmacies and 503B outsourcing facilities; an editor-in-chief of a leading compounding journal; nonprofit medical and pharmaceutical societies and organizations; compounding advocacy organizations; and nonprofit wellness organizations; women's health advocacy groups; and medical prescribers and researchers of cBHT. Several testimonies, position statements, and letters were also submitted by American Society for Reproductive Medicine, Endocrine Society, Alliance for Natural Health, Alliance for

Pharmacy Compounding, National Community Pharmacists Association, American Pharmacists Association, International Academy of Compounding Pharmacists, Reed Smith LLP, Congressmen Mark Pocan and Chris Stewart, Senator Lamar Alexander, and thousands of patients and professional advocates of cBHT.

COMMITTEE REQUEST FOR INFORMATION ON cBHT PREFERENCE AND USE

A "Dear Stakeholder" letter was emailed to a diverse group of study stakeholders in the summer of 2019.[1] The letter invited the stakeholders to disseminate questionnaire links to their membership networks and/or followers in order to gather public input on the use of cBHT from three relevant populations: consumers, providers, and pharmacists and compounders.

A total of 3,370 respondents who self-identified as consumers initiated the questionnaire, and 2,068 completed it; 327 respondents who self-identified as prescribers started the questionnaire, and 180 finished it; and 386 respondents who self-identified as pharmacists or compounders began the questionnaire with 166 completing it. Although the majority of responses came from the United States, a portion of the overall input was received from the international community.

The questionnaire was not designed to capture a nationally representative sample of consumers, prescribers, or compounders, and therefore, likely has a high risk of selection bias. As a result of this confound, the questionnaire cannot be used to provide quantitative data to inform the conclusions on the use of cBHT. Instead, the committee used the qualitative responses as testimonial evidence to better understand overall perspectives on cBHT use and preference, evidence that is difficult to derive from the current evidence base.

Summary of Responses

Respondents Who Identified as Consumers

Respondents to the consumer questionnaire reported first learning about options for cBHT use from sources that included their physician and through word of mouth from other sources. Similarly, respondents reported relying on their physicians, as well as Internet sources, books,

[1] Stakeholders included medical societies, wellness centers and organizations, women's health organizations, pharmacy associations, compounding organizations, government agencies, and education and research institutions.

and scientific literature, for information related to the potential safety and effectiveness of both cBHT and FDA-approved hormone therapy. Certain respondents expressed a lack of concern for the quality, safety, or effectiveness of cBHT preparations, while at the same time, also expressing concern for the quality, safety, and effectiveness of FDA-approved hormone therapy. Respondents who were satisfied with their use of cBHT tended to describe their satisfaction in terms of a preference for natural medications, overall improved well-being, and little to no adverse reactions.

Respondents Who Identified as Prescribers

Respondents who responded to the prescriber questionnaire specialized in fields including family medicine, obstetrics and gynecology, and wellness. Similarly, respondents represented various medical professions, including doctors of medicine (M.D.), doctors of osteopathy (D.O.), and nurse practitioners. Certain respondents expressed a lack of concern for the safety, product labeling, or quality of cBHT preparations, and reported a reliance on clinical trial data, professional experience, and patient response for evaluations on the safety and effectiveness of cBHT. Respondents varied widely in the types of circumstances they believed were appropriate to prescribe cBHT, in lieu of FDA-approved hormone therapy products. Certain respondents reported that they would prescribe only cBHT to their patients, while others described a narrow set of circumstances that would lead them to prescribe cBHT, in lieu of FDA-approved hormone therapies.

Respondents Who Identified as Pharmacists or Compounders

The respondents to the pharmacist and compounder questionnaire described a reliance on both published literature and professional experience for evidence on the potential safety and effectiveness of cBHT preparations. Resources for patients that describe the safety of cBHT formations varied—some respondents only provided oral instructions for use, others shared resources from compounding trade organizations, and still others distributed written information and instructions that were developed in house. Some respondents expressed having minimal concerns with the safety, labeling, or quality of cBHT preparations, while others stated that all hormones have risks.

Appendix B

Study Methods

LITERATURE REVIEW

In coordination with one of the National Academies' senior research librarians, the committee constructed a literature search strategy (see Figure B-1) that would produce an evidence-based body of research that could inform its work. A preliminary search (Search 1) queried six databases (Medline, Embase, PubMed, Scopus, ClinicalTrials.gov, and Toxnet) for content related to the safety, effectiveness, and clinical use of compounded bioidentical hormone therapy (cBHT). Results from Search 1 were limited to peer-reviewed articles published in the English language without any date restrictions, including human, animal, and in vitro studies. Editorials, commentaries, letters, and notes were excluded. This search resulted in 16,874 articles. Given the lack of specificity of the first search, in a second search (Search 2), the committee decided to expand and restrict certain search terms in order to produce a more relevant literature base. With all other search parameters remaining the same, this second search provided 11,224 articles with potential relevance to the committee's charge.

Of these 11,224 articles, those that included the terms *compounding*, *compounded*, *bioidentical*, or *bio-identical* and one of the 10 evaluated hormones in the title, keywords, or abstract were considered by the committee. Applying these criteria provided the committee with less than 50 articles to review. Of note, there are a number of articles with relevance to multiple hormones.

In order to complement the committee's search for literature related to the clinical utility of cBHT, the committee commissioned three additional

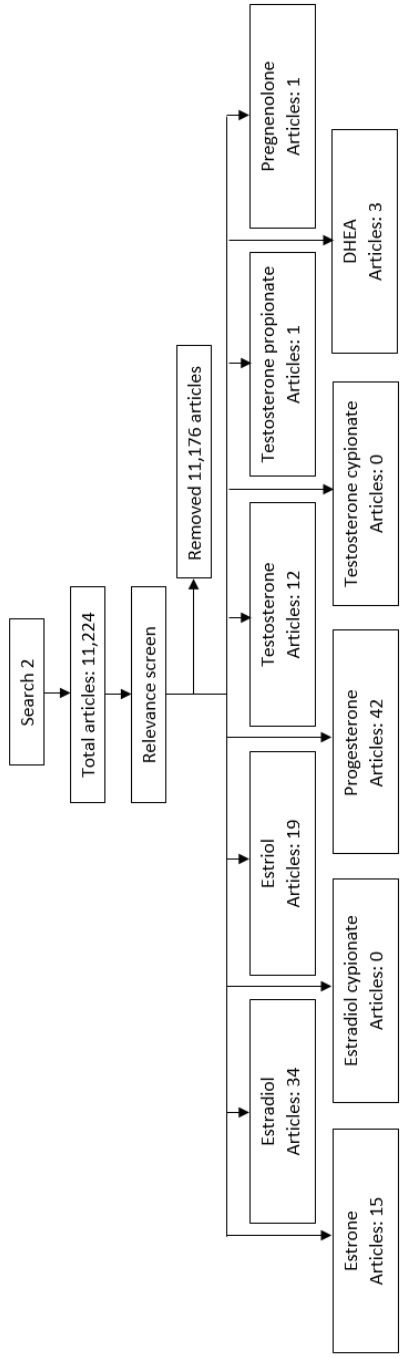

FIGURE B-1 Literature search and article selection process flowchart for literature on the safety and effectiveness of cBHT.

literature searches by the National Academies Research Center. Search 3 probed Embase, Medline, PubMed, Scopus, and Google for position statements on hormone therapy. Search 4 queried the Lexis Nexis database for federal and state cases, federal bills, the *Federal Register*, and law reviews for content related to cBHT. Search 5 explored Open Access Theses and Dissertations, ProQuest, and WorldCat Dissertations and Theses to identify theses and dissertations that could inform the committee's understanding of the clinical use of cBHT. A further search of ClinicalTrials.gov, the European Union Clinical Trials Register, and the World Health Organization International Clinical Trials Registry Platform was performed, but no additional studies were identified from this query.[1]

Assessment of the Literature

Search Strategies

Preliminary Search
Date performed: February 6, 2019
Articles obtained: 16,874

Databases: Embase, Medline, PubMed, Scopus, Toxnet, ClinicalTrials.gov

Search Parameters:
1900 to present
Peer-reviewed articles
English language
International

Search Terms:
1. "Bioidentical Hormone Replacement Therapy"
2. Biosimilar Pharmaceuticals
    a. biosimilar pharmaceuticals/administration and dosage
3. Hormone Replacement Therapy
    a. dehydroepiandrosterone
    b. estradiol
    c. estradiol cypionate

[1] In addition to the formal literature searches, study stakeholders, including the U.S. Food and Drug Administration, Professional Compounding Centers of America, representatives of select 503B outsourcing facilities, nonprofit professional organizations, and practicing medical prescribers of cBHT also submitted suggested articles and other references for the committee's review. Furthermore, during the National Academies' external review process, additional articles were suggested by reviewers of the report. Based on the criteria described above, all relevant articles were added to the total body of collected peer-reviewed evidence.

   d. estriol
   e. estrogens
   f. estrone
   g. pregnenolone
   h. progesterone
   i. testosterone
   j. testosterone cypionate
   k. testosterone propionate
4. Outcomes
   a. drug-related side effects and adverse reactions
   b. effectiveness, efficacy
   c. safety
5. Drug Compounding
6. Complex Mixtures
7. Biological Medicines
8. Specific Groups or Procedures
   a. adolescents (13–19 years old)
   b. pre and/or postmenopause
   c. sex reassignment
   d. antigens

Refined Search
Date performed: March 19, 2019
Articles obtained: 11,224

Databases: Embase, Medline, PubMed, Scopus, Toxnet, ClinicalTrials.gov

Search Parameters:
1900 to present
Peer-reviewed articles
English language
International

Search Terms:
1. Hormone Replacement Therapy
   a. dehydroepiandrosterone
   b. estradiol
   c. estradiol cypionate
   d. estriol
   e. estrone
   f. pregnenolone
   g. progesterone
   h. testosterone

   i. testosterone cypionate
   j. testosterone propionate
2. Outcomes
   a. drug-related side effects and adverse reactions
   b. effectiveness, efficacy
   c. safety
3. Drug Compounding
4. Bioidentical
5. Specific Groups or Procedures
   a. adolescents (13–19 years old)
   b. pre and/or postmenopause
   c. sex reassignment
   d. autoimmune disease
   e. cardiovascular risk
   f. breast cancer
   g. hypoactive sexual desire

Position Statement Search
Date performed: March 19, 2019
Articles obtained: 410

Databases: Embase, Medline, PubMed, Scopus, Google

Search Terms:
1. Hormone
2. Position Statement
3. Organization (only included in Google searches)

Legal Document Search
Date performed: April 24,2019
Documents obtained: 5,983

Database: Lexis Nexis

Search Parameters:
No date restrictions
Federal and state cases, combined
Federal Register, all
U.S. law reviews and journals, combined
Congressional Record, 1985–current
Federal full text of bills
State full text of bills
Federal bill tracking
State bill tracking

Search Terms:
1. Dehydroepiandrosterone
2. Estradiol
3. Estradiol Cypionate
4. Estriol
5. Estrone
6. Pregnenolone
7. Progesterone
8. Testosterone
9. Testosterone Cypionate
10. Testosterone Propionate

Dissertation and Thesis Search
Date performed: July 24, 2019
Articles obtained: 62

Databases: Open Access Theses and Dissertations,
ProQuest Research Library, WorldCat Dissertations and Theses

Search Parameters:
No date restrictions
Dissertations
English language
International
Human subjects

Search Terms:
1. Hormone Replacement Therapy
2. Hormones
    a. dehydroepiandrosterone
    b. estradiol
    c. estradiol cypionate
    d. estriol
    e. estrone
    f. pregnenolone
    g. progesterone
    h. testosterone
    i. testosterone cypionate
    j. testosterone propionate
3. Drug Compounding OR Bioidentical
4. Physicians' Practice Patterns
5. Attitude to Health
6. Side Effects OR Effectiveness OR Safety

Clinical Trials Search
Date performed: May 29, 2019
Trials obtained: 77

Databases: ClinicalTrials.gov,
World Health Organization International Clinical Trials Registry Platform,
European Union Clinical Trials Register

Search Parameters:
No date restrictions
International
All study phases

Search Terms:
1. Hormones
    a. dehydroepiandrosterone
    b. estradiol
    c. estradiol cypionate
    d. estriol
    e. estrone
    f. pregnenolone
    g. progesterone
    h. testosterone
    i. testosterone cypionate
    j. testosterone propionate
2. Drug Compounding OR Bioidentical

Appendix C

Glossary

active pharmaceutical ingredient (API): Any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure and function of the body of humans or other animals. Elements of a drug that are not an API are called inert pharmaceutical ingredients.[1,2]

adverse event: An adverse event is any undesirable experience associated with the use of a medical product or preparation in a patient.[2]

andropause: Also termed "late-onset hypogonadism," "testosterone deficiency syndrome," and colloquially, "male menopause," is a decrease in androgens, especially testosterone, in males that is associated with aging. The origin may be hypothalamic or pituitary (central), testicular, or a combination of both.

bioavailability: The fraction of the administered dose of a drug that reaches the bloodstream for systemic circulation.

[1] Definition from the United States Pharmacopeia.
[2] Definition adapted from the U.S. Food and Drug Administration.

bioequivalence: The therapeutic and pharmacokinetic uniformity of two drug products delivered at the same molar dose and under the same conditions.

bioidentical: Sometimes referred to as "bio-identical" or "bio identical," bioidentical describes hormones that are chemically and structurally identical to those produced by the human body, with the implication that an identical structure translates to an identical physiologic response as endogenous hormones. Bioidentical hormones may be synthesized from plant or animal sources, or completely chemically synthesized; they are offered as U.S. Food and Drug Administration (FDA)-approved products, or products that have not undergone FDA approval.

bulk drug substance: Any substance that is intended for incorporation into a finished drug product or preparation and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body, but the term does not include intermediates used in the synthesis of such substances.[2]

clinical need: When used in this report, "clinical need" refers to the condition outlined by Congress in section 503B of the Federal Food, Drug, and Cosmetic Act as amended by the Drug Quality and Security Act of 2013 that prohibits 503B outsourcing facilities from compounding with a bulk drug substance unless the substance appears on a list established by the U.S. Food and Drug Administration (FDA) identifying which bulk drug substances there is a clinical need for (understood to be when there is no FDA-approved product available to treat the indication the drug is being compounded for).

clinical trial: Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

clinical utility: A multidimensional construct that reflects evidence about safety, effectiveness, and therapeutic need.[3] Patient preference is also a component, and reflects patients' individual decision-making, based on variable acceptance of benefits and risks.

compounded preparation: A nonsterile or sterile drug or nutrient preparation that is formulated in a licensed pharmacy, outsourcing facility, or other

[3] In the context of this report, *therapeutic need* relates to the treatment of menopausal and male hypogonadism symptoms.

health care–related facility in response to or anticipation of a prescription or a medication order from a licensed prescriber. Federal law permits compounding; however, these drugs are not U.S. Food and Drug Administration approved for safety and effectiveness.

compounder: An individual who makes compounded preparations. Compounders can be pharmacists, physicians, or individuals under the supervision of a pharmacist, and they may practice in a variety of health care facilities, including pharmacies, hospitals, clinics, and outsourcing facilities.

compounding: Drug compounding is often regarded as the process of combining, mixing, or altering ingredients to create a medication tailored to the needs of an individual patient. Compounding includes the combining of two or more drugs. Compounded drugs are not U.S. Food and Drug Administration approved.[2]

compounding pharmacy: A pharmacy that makes compounded preparations in response to or anticipation of a prescription order for an individual patient.

conventional hormone therapy: In regard to hormone therapy, conventional refers to U.S. Food and Drug Administration–approved (or equivalent regulatory body) products, which may include conjugated estrogens, progestins, or bioidenticals.

difficult to compound: A condition of both sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act that precludes the use in compounding of those drugs appearing on the list of drugs with a demonstrable difficulty to compound.

drug: For the purposes of this report, considered a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease by affecting the structure or any function of the body.

endogenous: A reference to the originating source of a substance being within the human body.

estrogen: Hormones that bind to estrogen receptors in humans, and exert estrogenic activity. Endogenous estrogens include estrone, estradiol, and estriol.

evidence based: Evidence for efficacy or effectiveness should be based on designs that provide significant confidence in the results. The highest level

of confidence is provided by multiple, well-conducted randomized experimental trials, and their combined inferences should be used in most cases. When evaluations with such experimental designs are not available, evidence for efficacy or effectiveness cannot be considered definitive.

evidence-based medicine: To the greatest extent possible, the decisions that shape the health and health care of Americans—by patients, providers, payers, and policy makers alike—will be grounded on a reliable evidence base, will account appropriately for individual variation in patient needs, and will support the generation of new insights on clinical effectiveness.

excipient: A pharmacologically inactive ingredient used in the formulation of a drug that lends various functional properties to the drug formulation (i.e., dosage form, drug release, etc.).

exogenous: A reference to the originating source of a substance being from outside the human body.

FDA-approved drug product: The finished dosage form that contains a drug substance, generally, but not necessarily in association with other active or inactive ingredients, and has received U.S. Food and Drug Administration (FDA) approval for safety and effectiveness. An FDA-approved drug product will appear in FDA's *Orange Book*.

formulation: A selection and mixture of active pharmaceutical ingredients and inactive ingredients, which ideally takes stability, form, and strength into consideration.

hazardous drugs: Any drug identified by at least one of the following criteria: (1) carcinogenicity, teratogenicity, or developmental toxicity; (2) reproductive toxicity in humans; (3) organ toxicity at low dose in humans or animals; and (4) genotoxicity or new drugs that mimic existing hazardous drugs in structure or toxicity. Sites that compound hazardous drugs are required to comply with specific facilities and engineering controls.[1]

hormone: A diverse class of molecules that influence the activity of other cells throughout the human body. They are excreted from various tissues, circulate in the blood throughout the body, and influence different physiological responses by generating cellular signals through their interactions with ion channels or by binding to and activating a class of proteins called receptors.

hormone pellet: An implant that is inserted subcutaneously and delivers hormones to the body over an extended period of time.

hormone replacement therapy: Though often used synonymously with "hormone therapy," hormone replacement may connote an intent to restore hormone levels to what they were previous to the individual becoming symptomatic. However, based on clinical guidance, the goal of U.S. Food and Drug Administration–approved therapeutic treatment with hormones is to alleviate symptoms and clinical findings.

hormone therapy: A therapeutic treatment that alters the levels of hormones in the body in order to alleviate symptomology.

hot flushes: Also termed "hot flashes," are recurring, sudden and exaggerated sensation of warmth, especially on the face, neck, and chest. Skin may also become reddened at the affected site.

inert pharmaceutical ingredients: An inert, or inactive, ingredient is any substance, other than an "active" ingredient, which is intentionally included in a product. The term "inert" does not imply that the chemical is nontoxic.

mechanism of action: Describes the process by which a drug functions to produce a pharmacological effect.

menopause: A natural event marked by the permanent end of menstruation and fertility due to reduced ovarian function and subsequent decreases in ovarian hormones, confirmed after 12 consecutive months without menstruation.

natural: Describes a hormone drug product derived from a naturally occurring steroid that requires no chemical modification for human administration.

night sweats: Recurring episodes of intense perspiration during sleep, irrelevant of ambient temperature.

off-label: A drug is considered off-label for example when an approved drug product is prescribed for a condition, or in a dose, other than that for which it received its approval.

outsourcing facility: A facility that is engaged in the compounding of nonsterile or sterile drugs that has elected to register as an outsourcing facility per requirements of section 503B of the Federal Food, Drug, and Cosmetic Act. An outsourcing facility may or may not obtain prescriptions for identified individual patients.

pharmacokinetics: The science of drug absorption, distribution, metabolism, and excretion.

progesterone: A hormone produced in the human body by the corpus luteum, placenta, and adrenal cortex that exerts its role in preparing the uterus for pregnancy.

progestin: Hormones with progestogenic activity that are synthesized from various hormone starting materials and bind to progesterone receptors and exert the same effect as endogenous progesterone.

progestogen: Hormones that bind to progesterone receptors in humans and exert progestogenic (endogenous progesterone-like) activity. Progestogens include progesterone and progestins.

semisynthetic: Describes a hormone derived from a naturally ocurring steroid or sterol that requires chemical synthesis for human administration (e.g., hormones derived from soy and Mexican yams).

synthetic: Describes a hormone that is chemically synthesized from non-steroidal starting material.

vaginal implant: A medicated object, usually a plastic ring, which is inserted into the vagina for slow, long-term absorption of the active drug(s). Unlike vaginal suppositories or tablets, vaginal implants are not completely dissolved in the vagina and must be removed after a specified duration of time.

vaginal suppository: A drug delivery method that relies on the temperature of the body to melt the solid, waxy base in which the active drug is contained, allowing the drug to be absorbed directly into the vaginal walls.

vaginal tablet: Sometimes called a "vaginal insert," is similar in appearance to an oral pill or tablet, but it is inserted into the vagina for absorption.

vasomotor symptoms: Both hot flushes and night sweats are considered to be vasomotor symptoms.

vulvovaginal atrophy: Also known by the terms "vaginal atrophy," "atrophic vaginitis," and "urogenital atrophy," vulvovaginal atrophy is a thinning, drying, and inflammation of the vaginal tissue due to decreased estrogen presence in these tissues. Vulvovaginal atrophy most commonly occurs in postmenopausal females, and may consist of one or more of the following symptoms: dryness, itching, irritation, soreness, burning, pain during vaginal intercourse, urinary frequency and/or urgency, urge incontinence, burning sensation during urination, and inability to control urine flow.

Appendix D

Biosketches

COMMITTEE MEMBERS

Donald R. Mattison, M.D. (*Chair*), was appointed Chief Medical Officer of Risk Sciences International in 2012. Dr. Mattison also serves as Associate Director of the McLaughlin Centre for Population Health Risk Assessment at the University of Ottawa, Research Fellow of the International Prevention Research Institute, and Member of the QuarterWatch Team, Institute for Safe Medication Practice. He has held academic, clinical, and research appointments, including Senior Advisor to the Director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Medical Director of the March of Dimes; Dean of the Graduate School of Public Health at the University of Pittsburgh, Professor of Obstetrics and Gynecology and Interdisciplinary Toxicology at the University of Arkansas for Medical Sciences, and Director of Human Risk Assessment at the U.S. Food and Drug Administration National Center for Toxicological Research. Mattison earned a B.A. (chemistry and mathematics) from Augsburg College in Minneapolis, Minnesota; an M.S. (chemistry) from the Massachusetts Institute of Technology in Cambridge, Massachusetts; and an M.D. from the Vagelos College of Physicians and Surgeons, Columbia University, New York. His clinical training in Obstetrics and Gynecology was at the Sloane Hospital for Women in the Columbia Presbyterian Medical Center in New York. His training in pharmacology and toxicology was at the National Institutes of Health in Bethesda, Maryland. He has published more than 250 peer-reviewed publications, as well as edited more than 10 monographs and books. In 1997, he was elected a Fellow of the American Association for the

Advancement of Science; in 1999, a Fellow of The New York Academy of Medicine; and in 2000, a member of the National Academy of Medicine. In 2005 he became a Distinguished Alumni of Augsburg College and in 2009 a Fellow of the Royal Society of Medicine.

Ruth M. Parker, M.D. (*Vice Chair*), is Professor of Medicine and Pediatrics at the Emory University School of Medicine and holds a secondary appointment at the Emory University School of Public Health in the Division of Epidemiology. Dr. Parker's primary research interests and activities have been in the area of medical education and health services of underserved populations. She has been actively involved in medical education and faculty development since joining the medical school faculty. For more than two decades, Dr. Parker has focused extensively on health care issues of underserved populations, particularly health literacy. She was a principal investigator in the Robert Wood Johnson Foundation Literacy in Health Study and helped create a widely used measurement tool to quantify patients' ability to read and understand health information (TOFHLA, the Test Of Functional Health Literacy in Adults). She has authored numerous papers on health literacy and co-edited the complete bibliography of medicine on health literacy for the National Library of Medicine. She co-authored the most widely used definition of health literacy, which was used in *Healthy People 2010* and *Healthy People 2020* and is currently used by the National Academies and by the National Institutes of Health. Dr. Parker currently serves as consultant and advisor to numerous federal agencies, professional societies, and members of industry on their initiatives related to health literacy. Dr. Parker attended Davidson College and received her medical training at the University of North Carolina at Chapel Hill. She completed her residency and chief residency at the Strong Memorial Hospital in Rochester, New York, and her fellowship as a Robert Wood Johnson Foundation Clinical Scholar at the University of Pennsylvania. She holds board certification in both internal medicine and pediatrics.

Lesley H. Curtis, Ph.D., is Professor and Chair of Population Health Sciences and Interim Director of the Duke Clinical Research Institute at Duke University. Dr. Curtis is a health services researcher who oversees a portfolio of projects that use observational data to address questions related to clinical and comparative effectiveness, pharmacoepidemiology, health care delivery, and epidemiological trends across a broad array of clinical conditions and clinical care settings. The Duke Clinical Research Institute has a number of professional connections with pharmaceutical companies, but it has not conducted trials on bioidentical hormone replacement therapy products. An expert in the use of Medicare claims data for health services and clinical outcomes research, she has led the linkage of Medicare claims

with several large clinical registries and epidemiological cohort studies including the Framingham Heart Study and the Cardiovascular Health Study. She leads the Distributed Research Network Operations Center for the Patient-Centered Outcomes Research Institute's National Clinical Research Network (PCORnet), working with health systems and patient networks to develop a harmonized data infrastructure for robust observational and interventional research.

Susan S. Ellenberg, Ph.D., is Professor of Biostatistics, Medical Ethics, and Health Policy at the University of Pennsylvania Perelman School of Medicine. Prior to joining Penn in 2004, Dr. Ellenberg held leadership positions at the National Institutes of Health and the U.S. Food and Drug Administration (FDA). Due to her appointment to FDA's Endocrinologic and Metabolic Advisory Committee, Dr. Ellenberg holds a Special Government Employee status. Her research interests have focused on issues in the design, conduct, and analysis of clinical trials, and on assessment of medical product safety. Particular areas of interest include efficient trial designs, interim monitoring, and the operation of data monitoring committees, evaluation of surrogate endpoints, ethical issues in clinical research, and special issues in trials of cancer and AIDS therapies, and of vaccines. In her work, Dr. Ellenberg works closely with several pharmaceutical companies, including Merck, Bristol-Myers Squibb, and Marinus Pharmaceuticals. She is Associate Editor of *Clinical Trials* and the *Journal of the National Cancer Institute*. Dr. Ellenberg is a Fellow of the American Statistical Association, the American Association for the Advancement of Science (AAAS), and the Society for Clinical Trials, and an elected member of the International Statistical Institute. She has served as President of the Society for Clinical Trials and the Eastern North American Region of the International Biometric Society, and has chaired the Statistics Section of AAAS and the Board of Trustees for the National Institute of Statistical Sciences. The second edition of her book on clinical trials data monitoring committees, co-authored with Thomas Fleming (University of Washington) and David DeMets (University of Wisconsin), released in January 2019.

Jennifer Fishman, Ph.D., is Associate Professor in the Biomedical Ethics Unit and the Department of the Social Studies of Medicine at McGill University. Dr. Fishman is a sociologist of science, technology, and medicine. She uses empirical qualitative methods to describe and analyze the emergence of new medical knowledge and technologies, from the early stages of development to their integration into clinical practice and dissemination to clinicians and patients. Often referred to as "empirical ethics," she analyzes the oft unexamined and presumptive ethics and values within new scientific enterprises and how these affect research trajectories, technological

diffusion and commercialization, and ultimately patients and consumers. She has studied new pharmaceutical drug development and advertising, antiaging science and medicine, direct-to-consumer genetic risk susceptibility testing, end-of-life medical decisions, prenatal genetic carrier testing panels, and the promise of personalized genomic medicine. In 2015, she co-authored the academic paper titled "Bioidentical Hormones, Menopausal Women, and the Lure of the 'Natural' in US Antiaging Medicine." Dr. Fishman received her Ph.D. in sociology at the University of California, San Francisco, and her B.A. at the University of California, Berkeley.

Adel H. Karara, Ph.D., FCP, is Professor of Pharmaceutical Sciences at University of Maryland, Eastern Shore (UMES), where he teaches in the areas of pharmaceutics, biopharmaceutics, and pharmacokinetics. Prior to joining UMES, he held senior positions in the pharmaceutical industry. His research had been primarily in the female health care area working on the pharmacokinetics/dynamics of combination hormone treatments. As Senior Clinical Pharmacologist at Roche, he had the responsibility for guiding the selection of early drug discovery compounds, due diligence projects, and design of clinical pharmacology development programs for several metabolic drug candidates. Before joining Roche, he was Director at Berlex where he provided NDA support for Yasmin, ClimaraPro, Menostar, and Angeliq. At Novartis, he provided support for Starlix, Lescol, and Neoral. Within these positions, Karara was largely responsible for the clinical pharmacological characterization of hormone products in clinical trials (specifically oral contraceptive/birth control products), data interpretation, and quality support. Dr. Karara was a tenured faculty at the University of Louisiana where he mentored three Ph.D. and two M.S. students and won the Researcher of the Year award. Dr. Karara is a Charter member of the American Association of Pharmaceutical Scientists (AAPS), participated in teaching short courses, and served on abstract screening committees. Dr. Karara was elected to serve as Chair of the Clinical Pharmacology and Translational Medicine Section of AAPS. He has 39 peer-reviewed publications and was invited speaker at several clinical pharmacology forums. He served on Pharmaceutical Research and Manufacturers of America, Clinical Pharmacology Technical Group, where he led the exploratory Investigational New Drug survey initiative. Dr. Karara currently serves on the U.S. Food and Drug Administration Pharmaceutical Science and Clinical Pharmacology Advisory Committee for oncology drugs (ODAC). Dr. Karara is a Fellow of the American College of Clinical Pharmacology and serves on the editorial board of the *Journal of Clinical Pharmacology*.

Aaron S. Kesselheim, M.D., J.D., M.P.H., is Professor of Medicine at the Harvard Medical School (HMS) and a faculty member in the Division

of Pharmacoepidemiology and Pharmacoeconomics in the Department of Medicine at Brigham and Women's Hospital (BWH). He is board certified in internal medicine, and serves as a primary care physician at the Phyllis Jen Center for Primary Care at BWH. Within the division, Dr. Kesselheim created and leads the Program on Regulation, Therapeutics, And Law (PORTAL), an interdisciplinary research core focusing on intersections among prescription drugs and medical devices, patient health outcomes, and regulatory practices and the law. His research has concentrated on the interaction of law and public health related to drug discovery, testing, and regulatory approval, using a combination of quantitative and qualitative research tools and normative study. As the author of more than 350 publications in the peer-reviewed medical and health policy literatures, Dr. Kesselheim was recently recognized as the second most-cited health law scholar in Web of Science from 2013 to 2017. He has testified before Congress a half-dozen times on pharmaceutical policy, medical device regulation, generic drugs, and modernizing clinical trials; is a member of the U.S. Food and Drug Administration (FDA) Peripheral and Central Nervous System Advisory Committee; and served on a National Academies of Science, Engineering and Medicine consensus study committee on addressing the opioid epidemic. Dr. Kesselheim is a core faculty member at the HMS Center for Bioethics, where he co-teaches a course on health policy, law, and bioethics and organizes a popular monthly policy and ethics seminar series. Dr. Kesselheim also serves as the Irving S. Ribicoff Visiting Associate Professor of Law at Yale Law School, where he teaches a yearly course on FDA law. He serves on the Perspectives Advisory Board of the *New England Journal of Medicine* and is Editor-in-Chief of the *Journal of Law, Medicine & Ethics*.

Robert B. MacArthur, Pharm.D., M.S., is currently Pharmacy Director at The Rockefeller University Hospital, and a member of the Hospital Senior Staff, Institutional Review Board, and Clinical Translational Science Review Committee. He is also President of Orphan Drug Services, Inc., which provides drug development and statistics services to pharmaceutical companies and academic researchers. For more than 30 years Dr. MacArthur has been continuously engaged in the fields of commercial drug development, clinical research, and research/hospital pharmacy practice. His work experience includes large pharma (Sandoz, Novartis), small/mid pharma (Systems Medicines, CTI, Aeson Therapeutics, Cancer Prevention Pharmaceuticals, others), commercial phase 1 units (LAB, Inc., others), GMP drug manufacturing (Pii Inc. US, PharmMaterials UK, others), and academia (Columbia University, Northeastern University, The Rockefeller University). In academia, as a Research and Hospital Pharmacy Director for more than 20 years, his work has enabled and supported many hundreds of studies,

and includes collaborating with many physician scientists. This includes compounding novel oral and injectable products for first-in-human/phase I/II/III studies, and distribution of study medications and supplies to research clinics in more than 30 countries. In 2003, Dr. MacArthur received a commendation from the National Institutes of Health (NIH) for his support of the ACCORD Clinical Trial. On behalf of clinical trial sponsors and investigators, Dr. MacArthur has worked with and presented to the U.S. Food and Drug Administration, EMA, NIH, the National Cancer Institute, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, patient groups, CROs, CDMOs, and others, always with the objective of moving a promising medication along the critical path toward regulatory approval. Over this time he has contributed to the development of many hundreds of human medicines, leading to multiple drug approvals in the United States and Europe.

José Manautou, Ph.D., is Professor of Toxicology and Interim Head of the Department of Pharmaceutical Sciences at the University of Connecticut. He was selected to serve on the National Advisory Environmental Health Sciences Council (NAEHSC), part of the National Institute of Environmental Health Sciences (NIEHS) in 2017. He has also served on the Board of Scientific Counselors within NIEHS. He is a world-renowned expert in acetaminophen hepatoxicity. Given his expertise, he is currently a member of the U.S. Food and Drug Administration's Nonprescription Drugs Advisory Committee. Dr. Manautou received his undergraduate degree in pharmacy from the University of Puerto Rico and his Ph.D. in pharmacology and toxicology from Purdue University. He came to the University of Connecticut as a postdoctoral researcher in 1992, working with pioneering toxicologist Professor Emeritus Steven Cohen. He was named a tenure track Assistant Professor in Toxicology in 1995, and received tenure and promotion to Associate Professor in 2001.

Nancy King Reame, Ph.D., M.S.N., is the Mary Lindsay Professor Emerita of Health Promotion and Risk Reduction in the School of Nursing at Columbia University in New York City. From 2005 to 2015, she directed the Pilot Studies Resource of the Irving Institute for Clinical and Translational Research in the College of Physicians and Surgeons and was Director of the Ph.D. program in Nursing. From 1980 to 2005, she held faculty posts at the University of Michigan in the School of Nursing and the Department of Obstetrics-Gynecology in the School of Medicine. Reame's research is focused on the effect of reproductive neuroendocrinology on women's health across the life span. Current studies include the role of menopause on cognition and HIV symptoms, and the effect of endometriosis on menstrual cycle phenotypes. A member of the National Academy of Medicine, Dr.

Reame is a women's health advocate, having served on the advisory committee to the National Institutes of Health's Women's Health Initiative, and as advisor for many years to the Boston Women's Health Book Collective for the iconic book, *Our Bodies, Ourselves*. She is certified as a menopause clinician and served as a past member of the Board of Trustees for the North American Menopause Society (NAMS); however, did not serve as a co-author or reviewer for NAMS's recently released position statement on bioidentical hormone replacement therapy products. Dr. Reame received her undergraduate degree in nursing from Michigan State University, a master's degree as a clinical nurse specialist from Wayne State University College of Nursing, and a Ph.D. in physiology from the Wayne State University School of Medicine, with postdoctoral training in reproductive endocrinology at the University of Michigan School of Medicine.

David R. Rubinow, M.D., is the Meymandi Professor and Chair of the Department of Psychiatry at the University of North Carolina (UNC) at Chapel Hill's School of Medicine. Prior to being recruited to UNC, he was Clinical Director of the National Institute of Mental Health (NIMH) and Chief of the Behavioral Endocrinology Branch of NIMH. His research interests focus on neurobehavioral effects of gonadal steroids and how genetic variation contributes to differential behavioral response to changes in steroid signaling. Research methods used include administration of hormone superagonists and receptor blockers to manipulate the menstrual cycle and identify the central effects of gonadal steroids in isolation. These studies have demonstrated that, unlike mood disorders accompanying endocrinopathies, reproductive endocrine-related mood disorders represent abnormal responses to normal hormonal signals. Dr. Rubinow has professional and financial interests in Sage Therapeutics, a pharmaceutical company that primarily manufactures and distributes medications to treat central nervous system disorders (e.g., depression). Current National Institutes of Health (NIH)-funded studies include investigations of continuous oral contraceptive administration in menstrual cycle-related mood disorders, estradiol effects on cardiovascular risk and mood dysregulation during the perimenopause, and biomarkers of postpartum depression. Additionally, the UNC Women's Mood Disorders Program, which he directs, has the first and only NIH training fellowship in Women's Mood Disorders. On the basis of his research, he was inducted into the National Academy of Medicine in 2012. He received his B.A. from the University of Michigan in 1970 and his M.D. from the University of Connecticut Health Center in 1975.

Rulla Tamimi, Sc.D., is an interim Assistant Professor of Population Health Sciences and interim Assistant Professor of Epidemiology in Pathology and

Laboratory Medicine at Weill Cornell Medicine. Formally, an Associate Professor of Medicine at the Harvard Medical School. Dr. Tamimi aims to better understand breast cancer risk by incorporating biospecimens and molecular tools in epidemiologic studies. She and her team have led research on breast cancer, including work on lifestyle risk factors, biomarkers, genetics, and gene expression. She studies intermediate markers of breast cancer risk including benign breast disease and mammographic density as an approach to better understand early-life influences on breast cancer risk. Working with computer scientists, she and her group are identifying additional mammographic imaging features that predict risk of breast cancer. By leveraging molecular tools and intermediate markers of risk, Dr. Tamimi hopes to shed new light on our understanding of risk factors of breast cancer with the goal of identifying strategies for breast cancer prevention and improved risk assessment. She received her M.S. and Sc.D. from the Harvard T.H. Chan School of Public Health.

CONSULTANT

Joe Alper, M.S., has been a science writer and technology analyst for more than 40 years. He played a central role in planning and establishing the National Cancer Institute's (NCI's) Alliance for Nanotechnology in Cancer and Physical Sciences-Oncology Centers programs, as well as the National Institute of Mental Health's Decade of the Brain initiative, and has written numerous policy documents for the President's Council of Advisors on Science and Technology (PCAST); the National Academies of Sciences, Engineering, and Medicine; NCI; and the National Institutes of Health, as well as many other foundations, including the NBDA, and federal agencies. He has also served as a contributing correspondent for *Science*, *Nature Biotechnology*, and *Self* magazines, and has written for a variety of publications, including *The Atlantic Monthly*, *Harper's*, *The New York Times*, *The Washington Post*, and *National Geographic*, work for which he received numerous national writing awards. Sandwiched between his years as a magazine writer and science and health care policy writer, Mr. Alper was Senior Director of corporate communication and strategic planning for a publicly traded biotechnology company in Boulder, Colorado. He graduated from the University of Illinois at Urbana-Champaign with a B.S. in chemistry and received M.S. degrees in both biochemistry and agricultural journalism from the University of Wisconsin–Madison. He also completed graduate coursework in architecture and conservation biology at the University of Minnesota and photography at the Maryland Institute College of Art.

STAFF

Leigh Miles Jackson, Ph.D. (*Study Director*), is a Senior Program Officer on the Board on Health Sciences Policy (HSP) and serves as Study Director for two U.S. Food and Drug Administration (FDA)-sponsored consensus studies related to compounded drug product—one that focuses on the utility of treating patients with compounded bioidentical hormone therapy and another that focuses on the safety and effectiveness of compounded topical pain creams. Prior to her work on HSP, Dr. Jackson served on the Board on Higher Education and Workforce where she directed the consensus study report *Minority Serving Institutions: America's Underutilized Resource for Strengthening the STEM Workforce*. Prior to this, Dr. Jackson worked in the Health and Medicine Division and directed the consensus study reports *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research* and *Advancing the Power of Economic Evidence to Inform Investments in Children, Youth, and Families*. Prior to joining the National Academies, she was a developmental psychopathology and neurogenomics research fellow at Vanderbilt University, where she investigated the role of chronic sleep disturbance and specific epigenetic modifications on the health outcomes of adolescents. Dr. Jackson has a bachelor's degree in chemistry from Wake Forest University and a Ph.D. in molecular and systems pharmacology from Emory University.

Elizabeth Townsend, M.P.H., is an Associate Program Officer with the Board on Health Sciences Policy (HSP). Prior to joining HSP, Ms. Townsend served as a staff member on several consensus study reports for the Division of Behavioral and Social Sciences and Education, including *A Roadmap to Reducing Child Poverty*, *The Promise of Adolescence: Realizing Opportunity for All Youth*, and *A Decadal Survey of the Social and Behavioral Sciences: A Research Agenda for Advancing Intelligence Analysis*. Before her work at the National Academies, Ms. Townsend managed a youth suicide prevention program for the State of Maine. She holds a B.S. from Radford University and an M.P.H. from the University of Alabama at Birmingham.

Andrew March, M.P.H., is a Research Associate participating in his first two studies at the National Academies for two U.S. Food and Drug Administration–sponsored consensus study reports on compounded pharmaceuticals. He comes to the Board on Health Sciences Policy after completing his Master's in Public Health at the Universitat Pompeu Fabra in Barcelona. Mr. March received his bachelor's degree in biology and Spanish from Roanoke College. His previous research experience includes sickness absence trends in working women and health care access in migrant populations.

Justin Jones, M.A., is a Senior Program Assistant for the Board on Health Sciences Policy. He has a bachelor's degree in history from the University of Maryland and a Master's in Sociology from the University of Glasgow. His previous research experience focused on racial disparities within the LGBT community of Scotland and the gender pay gap among Scottish universities. Prior to working at the National Academies, he worked with several science, technology, engineering, and mathematics focused organizations including the National Science Foundation and the Association of American Medical Colleges.

Andrew M. Pope, Ph.D., is Director of the Board on Health Sciences Policy (HSP). He has a Ph.D. in physiology and biochemistry from the University of Maryland and has been a member of the National Academies of Sciences, Engineering, and Medicine staff since 1982 and the Health and Medicine Division (HMD) staff since 1989. His primary interests are science policy, biomedical ethics, and environmental and occupational influences on human health. During his tenure at the National Academies, Dr. Pope has directed numerous studies on topics that range from injury control, disability prevention, biologic markers to the protection of human subjects of research, National Institutes of Health priority-setting processes, organ procurement and transplantation policy, and the role of science and technology in countering terrorism. Since 1998, Dr. Pope has served as Director of HSP, which oversees and guides a program of activities that is intended to encourage and sustain the continuous vigor of the basic biomedical and clinical research enterprises needed to ensure and improve the health and resilience of the public. Ongoing activities include the Forums on Neuroscience and Nervous System Disorders, Genomics, Drug Discovery and Development, and Medical and Public Health Preparedness for Catastrophic Events. Dr. Pope is the recipient of HMD's Cecil Award and the National Academy of Sciences President's Special Achievement Award.

Appendix E

503A and 503B Distribution Supplement

503A

Total estimates of 503A pharmacies vary based largely on how a compounding pharmacy is defined. In a 2016 report, The Pew Charitable Trusts reported a total of more than 32,000 pharmacies in the United States that compound. This value was derived from the listing of pharmacies that report compounding functions in the National Council for Prescription Drug Programs Provider Database as of 2015. Submission of this information to the database was optional and may not represent the true (and current) number of pharmacies that compound (The Pew Charitable Trusts, 2016). However, this estimate does not provide clarity on the extent of compounding services offered. The American Pharmacist Association estimates there are approximately 7,500 pharmacies in the United States that *specialize* in compounding (APhA, 2020), a substantially lower estimate than the total 503A pharmacies that perform any compounding.

503B

The value of 503B outsourcing facilities are reflective of those registered with the U.S. Food and Drug Administration as of February 2020. See Table E-1.

TABLE E-1 Distribution of 503B Outsourcing Facilities by State

State	Registered 503B Outsourcing Facilities	State	Registered 503B Outsourcing Facilities
AK	0	MT	0
AL	2	NC	1
AR	4	ND	0
AZ	4	NE	0
CA	6	NH	0
CO	4	NJ	4
CT	2	NM	0
DC	0	NV	1
DE	0	NY	6
FL	9	OH	2
GA	0	OK	1
HI	0	OR	0
IA	0	PA	2
ID	1	RI	0
IL	0	SC	4
IN	0	SD	0
KS	2	TN	3
KY	0	TX	9
LA	0	UT	0
MA	2	VA	0
MD	0	VT	1
ME	0	WA	0
MI	0	WI	0
MN	1	WV	0
MO	2	WY	0
MS	0		

SOURCE: FDA, 2020.

REFERENCES

APhA (American Pharmacists Association). 2020. *Frequently asked questions about pharmaceutical compounding*. https://www.pharmacist.com/frequently-asked-questions-about-pharmaceutical-compounding (accessed February 2020).

FDA (U.S. Food and Drug Administration). 2020. *Registered outsourcing facilities*. https://www.fda.gov/drugs/human-drug-compounding/registered-outsourcing-facilities (accessed January 2020).

The Pew Charitable Trusts. 2016. *National assessment of state oversight of sterile drug compounding*. Philadelphia, PA: The Pew Charitable Trusts.

Appendix F

Compounded Bioidentical Hormone Therapy Formulations with a Single Active Ingredient

The table begins on the following page.

No.	Active Ingredient Present from Listing[a]	Dosage Form	All Reported Active Ingredients	All Reported Active Ingredient Strengths[b]
1	Dehydroepiandrosterone	Capsule	Dehydroepiandrosterone	10 mg
2	Dehydroepiandrosterone	Capsule	Dehydroepiandrosterone	50 mg
3	Dehydroepiandrosterone	Cream	Dehydroepiandrosterone	0.02
4	Dehydroepiandrosterone	Cream	Dehydroepiandrosterone	10 mg
5	Dehydroepiandrosterone	Cream	Dehydroepiandrosterone	10 mg/mL
6	Dehydroepiandrosterone	Cream	Dehydroepiandrosterone	5 mg/0.1mL
7	Dehydroepiandrosterone	Gel	Dehydroepiandrosterone	25 mg/mL
8	Dehydroepiandrosterone	Solution	Dehydroepiandrosterone	25 mg/0.25 mL
9	Dehydroepiandrosterone	Suppository	Dehydroepiandrosterone	13 mg
10	Estradiol	Capsule	Estradiol	0.3 mg
11	Estradiol	Capsule	Estradiol	0.5 mg
12	Estradiol	Capsule	Estradiol	1 mg
13	Estradiol	Capsule	Estradiol	2 mg
14	Estradiol	Cream	Estradiol	0.01 mg/1 mL
15	Estradiol	Cream	Estradiol	0.1 mg/1 g
16	Estradiol	Cream	Estradiol	0.1 mg/1 mL
17	Estradiol	Cream	Estradiol	0.1 mg/1 mL
18	Estradiol	Cream	Estradiol	0.128 mg/1 mL
19	Estradiol	Cream	Estradiol; Lidocaine Hydrochloride	0.2 mg/1 g; 50 mg/1 g
20	Estradiol	Cream	Estradiol	0.2 mg/1 mL
21	Estradiol	Cream	Estradiol; Lidocaine Hydrochloride	0.5 mg/1 g; 50 mg/1 g
22	Estradiol	Cream	Estradiol	0.5 mg/1 mL

23	Estradiol	Cream	Estradiol	0.6 mg/1 mL
24	Estradiol	Cream	Estradiol	0.625 mg/1 g
25	Estradiol	Cream	Estradiol	0.625 mg/1 mL
26	Estradiol	Cream	Estradiol	0.75 mg/1 mL
27	Estradiol	Cream	Estradiol	0.2%
28	Estradiol	Cream	Estradiol	1 mg/0.1 g
29	Estradiol	Cream	Estradiol	1 mg/1 g
30	Estradiol	Cream	Estradiol	1 mg/1 mL
31	Estradiol	Cream	Estradiol	1 mg/1 mL
32	Estradiol	Cream	Estradiol	1.25 mg/1 mL
33	Estradiol	Cream	Estradiol	1.75 mg/1 mL
34	Estradiol	Cream	Estradiol	2 mg/1 mL
35	Estradiol	Cream	Estradiol	2.5 mg/1 mL
36	Estradiol	Cream	Estradiol	3.6 mg/1 mL
37	Estradiol	Gel	Estradiol	—
38	Estradiol	Gel	Estradiol	0.2%
39	Estradiol	Gel	Estradiol	0.5 mg/mL
40	Estradiol	Gel	Estradiol	1 mg/0.1 mL
41	Estradiol	Gel	Estradiol	1 mg/1 mL
42	Estradiol	Gel	Estradiol	2 mg/mL
43	Estradiol	Injection	Estradiol	5 mg/mL
44	Estradiol	Lozenge	Estradiol	0.5 mg
45	Estradiol	Lozenge	Estradiol	1 mg

continued

No.	Active Ingredient Present from Listing[a]	Dosage Form	All Reported Active Ingredients	All Reported Active Ingredient Strengths[b]
46	Estradiol	Ointment	Estradiol	0.1 mg/1 g
47	Estradiol	Ointment	Estradiol	0.1 mg/1 g
48	Estradiol	Ointment	Estradiol	0.25 mg/1 g
49	Estradiol	Ointment	Estradiol	0.5 mg/1 g
50	Estradiol	Ointment	Estradiol	0.5 mg/1 g
51	Estradiol	Ointment	Estradiol; Lidocaine Hydrochloride	0.5 mg/1 g; 50 mg/1 g
52	Estradiol	Ointment	Estradiol; Lidocaine Hydrochloride	0.5 mg/1 g; 50 mg/1 g
53	Estradiol	Ointment	Betamethasone Dipropionate; Diazepam; Estradiol	1 mg/1 g; 5 mg/1 g; 0.5 mg/1 g
54	Estradiol	Pellet	Estradiol	10 mg
55	Estradiol	Pellet	Estradiol	10 mg
56	Estradiol	Pellet	Estradiol	10 mg
57	Estradiol	Pellet	Estradiol	10 mg/1 mg
58	Estradiol	Pellet	Estradiol	10 mg/1 mg
59	Estradiol	Pellet	Estradiol	10 mg/10 mg
60	Estradiol	Pellet	Estradiol	12.5 mg
61	Estradiol	Pellet	Estradiol	12.5 mg
62	Estradiol	Pellet	Estradiol	12.5 mg
63	Estradiol	Pellet	Estradiol	12.5 mg
64	Estradiol	Pellet	Estradiol	12.5 mg/1 mg
65	Estradiol	Pellet	Estradiol	12.5 mg/1 mg
66	Estradiol	Pellet	Estradiol	12.5 mg/12.5 mg

67	Estradiol	Pellet	Estradiol	15 mg
68	Estradiol	Pellet	Estradiol	15 mg
69	Estradiol	Pellet	Estradiol	15 mg
70	Estradiol	Pellet	Estradiol	15 mg/1 mg
71	Estradiol	Pellet	Estradiol	15 mg/1 mg
72	Estradiol	Pellet	Estradiol	15 mg/15 mg
73	Estradiol	Pellet	Estradiol	18 mg
74	Estradiol	Pellet	Estradiol	18 mg
75	Estradiol	Pellet	Estradiol	18 mg
76	Estradiol	Pellet	Estradiol	18 mg/1 mg
77	Estradiol	Pellet	Estradiol	18 mg/1 mg
78	Estradiol	Pellet	Estradiol	18 mg/18 mg
79	Estradiol	Pellet	Estradiol	20 mg
80	Estradiol	Pellet	Estradiol	20 mg
81	Estradiol	Pellet	Estradiol	20 mg
82	Estradiol	Pellet	Estradiol	20 mg/1 mg
83	Estradiol	Pellet	Estradiol	20 mg/1 mg
84	Estradiol	Pellet	Estradiol	20 mg/20 mg
85	Estradiol	Pellet	Estradiol	22 mg
86	Estradiol	Pellet	Estradiol	22 mg
87	Estradiol	Pellet	Estradiol	22 mg/1 mg
88	Estradiol	Pellet	Estradiol	22 mg/22 mg
89	Estradiol	Pellet	Estradiol	25 mg

continued

No.	Active Ingredient Present from Listing[a]	Dosage Form	All Reported Active Ingredients	All Reported Active Ingredient Strengths[b]
90	Estradiol	Pellet	Estradiol	25 mg
91	Estradiol	Pellet	Estradiol	25 mg
92	Estradiol	Pellet	Estradiol	25 mg
93	Estradiol	Pellet	Estradiol	25 mg
94	Estradiol	Pellet	Estradiol	25 mg/1 mg
95	Estradiol	Pellet	Estradiol	25 mg/1 mg
96	Estradiol	Pellet	Estradiol	25 mg/25 mg
97	Estradiol	Pellet	Estradiol	37.5 mg
98	Estradiol	Pellet	Estradiol	37.5 mg/37.5 mg
99	Estradiol	Pellet	Estradiol	50 mg
100	Estradiol	Pellet	Estradiol	50 mg/50 mg
101	Estradiol	Pellet	Estradiol	6 mg
102	Estradiol	Pellet	Estradiol	6 mg
103	Estradiol	Pellet	Estradiol	6 mg
104	Estradiol	Pellet	Estradiol	6 mg
105	Estradiol	Pellet	Estradiol	6 mg
106	Estradiol	Pellet	Estradiol	6 mg/1 mg
107	Estradiol	Pellet	Estradiol	6 mg/1 mg
108	Estradiol	Pellet	Estradiol	6 mg/6 mg
109	Estradiol	Pellet	Estradiol	75 mg
110	Estradiol	Solution	Estradiol	0.001
111	Estradiol	Suppository	Estradiol	1 mg

112	Estriol	Capsule	Estriol	0.5 mg
113	Estriol	Cream	Estriol	0.01
114	Estriol	Cream	Estriol	0.5 mg/1 g
115	Estriol	Cream	Estriol	0.5 mg/1 g
116	Estriol	Cream	Estriol	0.5 mg/1 mL
117	Estriol	Cream	Estriol	0.00025
118	Estriol	Cream	Estriol	0.0005
119	Estriol	Cream	Estriol	0.3 mg/1 g; 0.5 mg/1 g; 1.0 mg/1 g
120	Estriol	Cream	Estriol	1 mg/1 g
121	Estriol	Cream	Estriol	1 mg/1 g
122	Estriol	Cream	Estriol	1 mg/1 g
123	Estriol	Cream	Estriol	1 mg/1 mL
124	Estriol	Cream	Estriol	1 mg/1 mL
125	Estriol	Cream	Estriol	1.5 mg/1 mL
126	Estriol	Cream	Estriol	2 mg/1 g
127	Estriol	Cream	Estriol	2 mg/1 g
128	Estriol	Cream	Estriol	2 mg/1 g
129	Estriol	Cream	Estriol	2.5 mg/1 g
130	Estriol	Cream	Estriol	3 mg/1 g
131	Estriol	Cream	Estriol	6 mg/1 g
132	Estriol	Gel	Estriol	0.2 mg/mL
133	Estriol	Gel	Estriol	2 mg/mL
134	Estriol	Ointment	Estriol	0.5 mg/1 g

continued

No.	Active Ingredient Present from Listing[a]	Dosage Form	All Reported Active Ingredients	All Reported Active Ingredient Strengths[b]
135	Estriol	Ointment	Estriol	1 mg/1 g
136	Estriol	Ointment	Estriol	2 mg/1 g
137	Progesterone	Capsule	Progesterone	10 mg
138	Progesterone	Capsule	Progesterone	10 mg
139	Progesterone	Capsule	Progesterone	100 mg
140	Progesterone	Capsule	Progesterone	100 mg
141	Progesterone	Capsule	Progesterone	100 mg
142	Progesterone	Capsule	Progesterone	100 mg
143	Progesterone	Capsule	Progesterone	100 mg
144	Progesterone	Capsule	Progesterone	100 mg
145	Progesterone	Capsule	Progesterone	100 mg
146	Progesterone	Capsule	Progesterone	100 mg
147	Progesterone	Capsule	Progesterone	100 mg
148	Progesterone	Capsule	Progesterone	100 mg
149	Progesterone	Capsule	Progesterone	100 mg
150	Progesterone	Capsule	Progesterone	100 mg
151	Progesterone	Capsule	Progesterone	12.5 mg
152	Progesterone	Capsule	Progesterone	120 mg
153	Progesterone	Capsule	Progesterone	125 mg
154	Progesterone	Capsule	Progesterone	125 mg
155	Progesterone	Capsule	Progesterone	125 mg

156	Progesterone	Capsule	Progesterone	135 mg
157	Progesterone	Capsule	Progesterone	150 mg
158	Progesterone	Capsule	Progesterone	150 mg
159	Progesterone	Capsule	Progesterone	150 mg
160	Progesterone	Capsule	Progesterone	150 mg
161	Progesterone	Capsule	Progesterone	150 mg
162	Progesterone	Capsule	Progesterone	165 mg
163	Progesterone	Capsule	Progesterone	175 mg
164	Progesterone	Capsule	Progesterone	175 mg
165	Progesterone	Capsule	Progesterone	20 mg
166	Progesterone	Capsule	Progesterone	200 mg
167	Progesterone	Capsule	Progesterone	200 mg
168	Progesterone	Capsule	Progesterone	200 mg
169	Progesterone	Capsule	Progesterone	200 mg
170	Progesterone	Capsule	Progesterone	200 mg; 100 mg; 50 mg
171	Progesterone	Capsule	Progesterone	210 mg
172	Progesterone	Capsule	Progesterone	225 mg
173	Progesterone	Capsule	Progesterone	25 mg
174	Progesterone	Capsule	Progesterone	25 mg
175	Progesterone	Capsule	Progesterone	250 mg
176	Progesterone	Capsule	Progesterone	300 mg
177	Progesterone	Capsule	Progesterone	35 mg
178	Progesterone	Capsule	Progesterone	40 mg

continued

No.	Active Ingredient Present from Listing[a]	Dosage Form	All Reported Active Ingredients	All Reported Active Ingredient Strengths[b]
179	Progesterone	Capsule	Progesterone	40 mg
180	Progesterone	Capsule	Melatonin; Progesterone	5 mg; 200 mg
181	Progesterone	Capsule	Progesterone	50 mg
182	Progesterone	Capsule	Progesterone	50 mg
183	Progesterone	Capsule	Progesterone	50 mg
184	Progesterone	Capsule	Progesterone	50 mg
185	Progesterone	Capsule	Progesterone	50 mg
186	Progesterone	Capsule	Progesterone	50 mg
187	Progesterone	Capsule	Progesterone	50 mg
188	Progesterone	Capsule	Progesterone	50 mg
189	Progesterone	Capsule	Progesterone	60 mg
190	Progesterone	Capsule	Progesterone	60 mg
191	Progesterone	Capsule	Progesterone	75 mg
192	Progesterone	Capsule	Progesterone	75 mg
193	Progesterone	Capsule	Progesterone	75 mg
194	Progesterone	Capsule	Progesterone	80 mg
195	Progesterone	Capsule, SR	Progesterone	50 mg capsule; 100 mg capsule; 200 mg capsule
196	Progesterone	Cream	Progesterone	0.05
197	Progesterone	Cream	Progesterone	0.1
198	Progesterone	Cream	Progesterone	0.1
199	Progesterone	Cream	Progesterone	0.1

200	Progesterone	Cream	Progesterone	0.0065%
201	Progesterone	Cream	Progesterone	10 mg/1 mL
202	Progesterone	Cream	Progesterone	100 mg/1 g
203	Progesterone	Cream	Progesterone	100 mg/1 g
204	Progesterone	Cream	Progesterone	100 mg/1 mL
205	Progesterone	Cream	Progesterone	100 mg/1 mL
206	Progesterone	Cream	Progesterone	120 mg/1 mL
207	Progesterone	Cream	Progesterone	125 mg/1 mL
208	Progesterone	Cream	Progesterone	150 mg/1 mL
209	Progesterone	Cream	Progesterone	160 mg/1 mL
210	Progesterone	Cream	Progesterone	175 mg/1 mL
211	Progesterone	Cream	Progesterone	20 mg/0.5 g
212	Progesterone	Cream	Progesterone	20 mg/0.5 g
213	Progesterone	Cream	Progesterone	20 mg/1 mL
214	Progesterone	Cream	Progesterone	20 mg/1 mL
215	Progesterone	Cream	Progesterone	20 mg/1 mL
216	Progesterone	Cream	Progesterone	200 mg/1 mL
217	Progesterone	Cream	Progesterone	200 mg/1 mL
218	Progesterone	Cream	Progesterone	200 mg/1 mL
219	Progesterone	Cream	Progesterone	20 mg/0.1 mL
220	Progesterone	Cream	Progesterone	25 mg/1 mL
221	Progesterone	Cream	Progesterone	250 mg/1 mL
222	Progesterone	Cream	Progesterone	25 mg; 50 mg; 75 mg; 100 mg

continued

No.	Active Ingredient Present from Listing[a]	Dosage Form	All Reported Active Ingredients	All Reported Active Ingredient Strengths[b]
223	Progesterone	Cream	Progesterone	30 mg/0.5 g
224	Progesterone	Cream	Progesterone	30 mg/1 mL
225	Progesterone	Cream	Progesterone	30 mg/1 mL
226	Progesterone	Cream	Progesterone	35 mg/1 mL
227	Progesterone	Cream	Progesterone	40 mg/1 mL
228	Progesterone	Cream	Progesterone	50 mg/1 mL
229	Progesterone	Cream	Progesterone	80 mg/1 mL
230	Progesterone	Cream	Progesterone	80 mg/1 mL
231	Progesterone	Cream	Progesterone	80 mg/1 mL
232	Progesterone	Enema	Progesterone	—
233	Progesterone	Gel	Progesterone	0.03
234	Progesterone	Gel	Progesterone	200 mg/1 mL
235	Progesterone	Gel	Progesterone	200 mg/mL
236	Progesterone	Gel	Progesterone	50 mg/mL
237	Progesterone	Lozenge	Progesterone	10 mg
238	Progesterone	Lozenge	Progesterone	100 mg
239	Progesterone	Lozenge	Progesterone	200 mg
240	Progesterone	Lozenge	Progesterone	200 mg
241	Progesterone	Lozenge	Progesterone	300 mg
242	Progesterone	Lozenge	Progesterone	400 mg
243	Progesterone	Lozenge	Progesterone	5 mg

244	Progesterone	Oil	Progesterone	60 mg/1 mL
245	Progesterone	Pellet	Progesterone	100 mg
246	Progesterone	Pellet	Progesterone	50 mg
247	Progesterone	Pellet	Progesterone	50 mg
248	Progesterone	Pellet	Progesterone	75 mg
249	Progesterone	Solution	Progesterone	100 mg/1 mL
250	Progesterone	Solution	Progesterone	100 mg/mL
251	Progesterone	Solution	Progesterone	40 mg/1 mL
252	Progesterone	Solution	Progesterone	40 mg/1 mL
253	Progesterone	Solution	Progesterone	50 mg/mL
254	Progesterone	Spray	Progesterone	0.02
255	Progesterone	Suppository	Progesterone	—
256	Progesterone	Suppository	Progesterone	—
257	Progesterone	Suppository	Progesterone	100 mg
258	Progesterone	Suppository	Progesterone	100 mg; 200 mg
259	Progesterone	Suppository	Progesterone	200 mg
260	Progesterone	Suppository	Progesterone	45 mg
261	Progesterone	Suppository	Progesterone	50 mg
262	Progesterone	Suppository	Progesterone	50 mg/mL
263	Progesterone	Suppository	Progesterone	50 mg; 100 mg; 200 mg
264	Progesterone	Suspension	Progesterone	200 mg/mL
265	Progesterone	Suspension	Progesterone	40 mg/mL
266	Progesterone	Tablet	Progesterone	200 mg

continued

No.	Active Ingredient Present from Listing[a]	Dosage Form	All Reported Active Ingredients	All Reported Active Ingredient Strengths[b]
267	Testosterone	Capsule	Testosterone	25 mg
268	Testosterone	Cream	Testosterone	0.3 mg/1 mL
269	Testosterone	Cream	Testosterone	0.5 mg/1 mL
270	Testosterone	Cream	Testosterone	0.5 mg; 1 mg; 2 mg; 3 mg
271	Testosterone	Cream	Testosterone	1 mg/1 mL
272	Testosterone	Cream	Testosterone	1.1 mg/1 mL
273	Testosterone	Cream	Testosterone	1.75 mg/1 mL
274	Testosterone	Cream	Testosterone	1.75 mg/1 mL
275	Testosterone	Cream	Testosterone	1.9 mg/1 mL
276	Testosterone	Cream	Testosterone	10 mg/1 g
277	Testosterone	Cream	Sildenafil Citrate; Testosterone	10 mg/1 g; 10 mg/1 g
278	Testosterone	Cream	Sildenafil Citrate; Arginine Hydrochloride; Testosterone; Ergoloid Mesylates; Pentoxifylline; Aminophylline	10 mg/1 g; 60 mg/1 g; 1 mg/1 g; 0.5 mg/1 g; 50 mg/1 g; 30 mg/1 g
279	Testosterone	Cream	Testosterone	10 mg/1 mL
280	Testosterone	Cream	Testosterone	100 mg/1 g
281	Testosterone	Cream	Testosterone	12 mg/1 mL
282	Testosterone	Cream	Testosterone	2 mg/1 mL
283	Testosterone	Cream	Testosterone	2.5 mg/1 g
284	Testosterone	Cream	Testosterone	2.5 mg/1 mL
285	Testosterone	Cream	Testosterone	20 mg/1 mL
286	Testosterone	Cream	Testosterone	20 mg/1 mL

287	Testosterone	Cream	Testosterone	200 mg/1 mL
288	Testosterone	Cream	Testosterone	3 mg/1 mL
289	Testosterone	Cream	Testosterone	3.5 mg/1 mL
290	Testosterone	Cream	Testosterone	4 mg/1 mL
291	Testosterone	Cream	Testosterone	40 mg/1 mL
292	Testosterone	Cream	Testosterone	5 mg/1 g
293	Testosterone	Cream	Testosterone	7.5 mg/1 mL
294	Testosterone	Cream	Testosterone	75 mg/1 g
295	Testosterone	Cream	Testosterone	8 mg/1 g
296	Testosterone	Cream	Testosterone	8 mg/1 mL
297	Testosterone	Gel	Testosterone	0.5 mg/1 mL
298	Testosterone	Gel	Testosterone	1 mg/0.1 mL
299	Testosterone	Gel	Testosterone	1 mg/0.1 mL
300	Testosterone	Gel	Testosterone	1 mg/1 g
301	Testosterone	Gel	Testosterone	1 mg/1 mL
302	Testosterone	Gel	Testosterone	1.25 mg/1 mL
303	Testosterone	Gel	Testosterone	1.5 mg/1 mL
304	Testosterone	Gel	Testosterone	100 mg/1 g
305	Testosterone	Gel	Testosterone	100 mg/1 g
306	Testosterone	Gel	Testosterone	100 mg/1 mL
307	Testosterone	Gel	Testosterone	100 mg/1 mL
308	Testosterone	Gel	Testosterone	12 mg/1 mL
309	Testosterone	Gel	Testosterone	2 mg/1 mL

continued

No.	Active Ingredient Present from Listing[a]	Dosage Form	All Reported Active Ingredients	All Reported Active Ingredient Strengths[b]
310	Testosterone	Gel	Testosterone	2.5 mg/1 mL
311	Testosterone	Gel	Testosterone	25 mg/1 mL
312	Testosterone	Gel	Testosterone	3 mg/1 mL
313	Testosterone	Gel	Testosterone	30 mg/1 mL
314	Testosterone	Gel	Testosterone	4 mg/1 mL
315	Testosterone	Gel	Testosterone	40 mg/1 mL
316	Testosterone	Gel	Testosterone	5 mg/1 mL
317	Testosterone	Gel	Testosterone	50 mg/1 g
318	Testosterone	Gel	Testosterone	50 mg/1 g
319	Testosterone	Gel	Testosterone	50 mg/1 g
320	Testosterone	Gel	Testosterone	50 mg/1 mL
321	Testosterone	Gel	Testosterone	50 mg/mL
322	Testosterone	Gel	Testosterone	6 mg/1 mL
323	Testosterone	Gel	Testosterone	8 mg/1 mL
324	Testosterone	Lotion	Testosterone	0.02
325	Testosterone	Lozenge	Testosterone	0.625 mg
326	Testosterone	Lozenge	Testosterone	1–10 mg
327	Testosterone	Lozenge	Testosterone	10 mg
328	Testosterone	Lozenge	Testosterone	1 mg
329	Testosterone	Lozenge	Testosterone	2 mg
330	Testosterone	Lozenge	Testosterone	3 mg
331	Testosterone	Ointment	Testosterone; Menthol	0.02

332	Testosterone	Ointment	Testosterone; Menthol	0.02
333	Testosterone	Ointment	Testosterone	10 mg/1 g
334	Testosterone	Ointment	Testosterone	20 mg/1 g
335	Testosterone	Pellet	Testosterone	100 mg
336	Testosterone	Pellet	Testosterone	100 mg
337	Testosterone	Pellet	Testosterone	100 mg
338	Testosterone	Pellet	Testosterone	100 mg
339	Testosterone	Pellet	Testosterone	100 mg
340	Testosterone	Pellet	Testosterone	100 mg
341	Testosterone	Pellet	Testosterone	100 mg
342	Testosterone	Pellet	Testosterone	100 mg
343	Testosterone	Pellet	Testosterone	100 mg/1 mg
344	Testosterone	Pellet	Testosterone	100 mg/1 mg
345	Testosterone	Pellet	Testosterone	100 mg/100 mg
346	Testosterone	Pellet	Testosterone; Anastrozole	100 mg; 4 mg
347	Testosterone	Pellet	Testosterone	12.5 mg
348	Testosterone	Pellet	Testosterone	12.5 mg
349	Testosterone	Pellet	Testosterone	12.5 mg
350	Testosterone	Pellet	Testosterone	12.5 mg
351	Testosterone	Pellet	Testosterone	12.5 mg
352	Testosterone	Pellet	Testosterone	12.5 mg
353	Testosterone	Pellet	Testosterone	12.5 mg/1 mg
354	Testosterone	Pellet	Testosterone	12.5 mg/1 mg

continued

No.	Active Ingredient Present from Listing[a]	Dosage Form	All Reported Active Ingredients	All Reported Active Ingredient Strengths[b]
355	Testosterone	Pellet	Testosterone	12.5 mg/1 mg
356	Testosterone	Pellet	Testosterone	18 mg
357	Testosterone	Pellet	Testosterone	18 mg
358	Testosterone	Pellet	Testosterone	18 mg/18 mg
359	Testosterone	Pellet	Testosterone	200 mg
360	Testosterone	Pellet	Testosterone	200 mg
361	Testosterone	Pellet	Testosterone	200 mg
362	Testosterone	Pellet	Testosterone	200 mg
363	Testosterone	Pellet	Testosterone	200 mg
364	Testosterone	Pellet	Testosterone	200 mg
365	Testosterone	Pellet	Testosterone	200 mg
366	Testosterone	Pellet	Testosterone	200 mg
367	Testosterone	Pellet	Testosterone	200 mg
368	Testosterone	Pellet	Testosterone	200 mg
369	Testosterone	Pellet	Testosterone	200 mg/1 mg
370	Testosterone	Pellet	Testosterone	200 mg/1 mg
371	Testosterone	Pellet	Testosterone	200 mg/200 mg
372	Testosterone	Pellet	Testosterone; Anastrozole	200 mg; 20 mg
373	Testosterone	Pellet	Testosterone; Anastrozole	200 mg; 20 mg
374	Testosterone	Pellet	Testosterone	25 mg
375	Testosterone	Pellet	Testosterone	25 mg
376	Testosterone	Pellet	Testosterone	25 mg

377	Testosterone	Pellet	Testosterone	25 mg
378	Testosterone	Pellet	Testosterone	25 mg
379	Testosterone	Pellet	Testosterone	25 mg
380	Testosterone	Pellet	Testosterone	25 mg/1 mg
381	Testosterone	Pellet	Testosterone	25 mg/1 mg
382	Testosterone	Pellet	Testosterone	25 mg/25 mg
383	Testosterone	Pellet	Testosterone	37.5 mg
384	Testosterone	Pellet	Testosterone	37.5 mg
385	Testosterone	Pellet	Testosterone	37.5 mg
386	Testosterone	Pellet	Testosterone	37.5 mg
387	Testosterone	Pellet	Testosterone	37.5 mg
388	Testosterone	Pellet	Testosterone	37.5 mg
389	Testosterone	Pellet	Testosterone	37.5 mg/1 mg
390	Testosterone	Pellet	Testosterone	37.5 mg/37.5 mg
391	Testosterone	Pellet	Anastrozole; Testosterone	4 mg/1 mg; 100 mg/1 mg
392	Testosterone	Pellet	Anastrozole; Testosterone	4 mg/1 mg; 60 mg/1 mg
393	Testosterone	Pellet	Anastrozole; Testosterone	4 mg/1 mg; 75 mg/1 mg
394	Testosterone	Pellet	Testosterone	40 mg/40 mg
395	Testosterone	Pellet	Testosterone	50 mg
396	Testosterone	Pellet	Testosterone	50 mg
397	Testosterone	Pellet	Testosterone	50 mg
398	Testosterone	Pellet	Testosterone	50 mg
399	Testosterone	Pellet	Testosterone	50 mg

continued

No.	Active Ingredient Present from Listing[a]	Dosage Form	All Reported Active Ingredients	All Reported Active Ingredient Strengths[b]
400	Testosterone	Pellet	Testosterone	50 mg
401	Testosterone	Pellet	Testosterone	50 mg/1 mg
402	Testosterone	Pellet	Testosterone	50 mg/1 mg
403	Testosterone	Pellet	Testosterone	50 mg/50 mg
404	Testosterone	Pellet	Testosterone	55 mg/55 mg
405	Testosterone	Pellet	Testosterone	60 mg/1 mg
406	Testosterone	Pellet	Testosterone; Anastrozole	60 mg; 4 mg
407	Testosterone	Pellet	Testosterone	62.5 mg
408	Testosterone	Pellet	Testosterone	62.5 mg
409	Testosterone	Pellet	Testosterone	62.5 mg
410	Testosterone	Pellet	Testosterone	70 mg
411	Testosterone	Pellet	Testosterone	70 mg
412	Testosterone	Pellet	Testosterone; Anastrozole	75 mg; 4 mg
413	Testosterone	Pellet	Anastrozole; Testosterone	8 mg/1 mg; 100 mg/1 mg
414	Testosterone	Pellet	Anastrozole; Testosterone	8 mg/1 mg; 100 mg/1 mg
415	Testosterone	Pellet	Testosterone	80 mg
416	Testosterone	Pellet	Testosterone	80 mg
417	Testosterone	Pellet	Testosterone	80 mg
418	Testosterone	Pellet	Testosterone	80 mg
419	Testosterone	Pellet	Testosterone	80 mg
420	Testosterone	Pellet	Testosterone	80 mg/1 mg
421	Testosterone	Pellet	Testosterone	87.5 mg

422	Testosterone	Pellet	Testosterone	87.5 mg
423	Testosterone	Pellet	Testosterone	87.5 mg
424	Testosterone	Pellet	Testosterone	87.5 mg
425	Testosterone	Pellet	Testosterone	87.5 mg
426	Testosterone	Pellet	Testosterone	87.5 mg/1 mg
427	Testosterone	Pellet	Testosterone	87.5 mg/1 mg
428	Testosterone	Pellet	Testosterone	87.5 mg/87.5 mg
429	Testosterone	Solution	Testosterone	10 mg/0.1 mL
430	Testosterone	Solution	Testosterone	25 mg/0.25 mL
431	Testosterone	Solution	Testosterone	5 mg/1 mL
432	Testosterone	Solution	Testosterone	50 mg/1 mL
433	Testosterone	Spray	Testosterone	1 mg/0.1 mL
434	Testosterone	Spray	Testosterone	1 mg/0.1 mL
435	Testosterone Cypionate	Injection	Testosterone Cypionate	0.2 g/1,000 g
436	Testosterone Cypionate	Injection	Testosterone Cypionate	0.2 g/1,000 g
437	Testosterone Cypionate	Injection	Testosterone Cypionate	0.2 g/1,000 g
438	Testosterone Cypionate	Injection	Testosterone Cypionate	100 mg/1 mL
439	Testosterone Cypionate	Injection	Testosterone Cypionate	100 mg/mL
440	Testosterone Cypionate	Injection	Testosterone Cypionate	150 mg/1 mL
441	Testosterone Cypionate	Injection	Testosterone Cypionate	200 mg/1 mL
442	Testosterone Cypionate	Injection	Testosterone Cypionate	200 mg/1 mL
443	Testosterone Cypionate	Injection	Testosterone Cypionate	200 mg/1 mL
444	Testosterone Cypionate	Injection	Testosterone Cypionate	200 mg/1 mL

continued

No.	Active Ingredient Present from Listing[a]	Dosage Form	All Reported Active Ingredients	All Reported Active Ingredient Strengths[b]
445	Testosterone Cypionate	Injection	Testosterone Cypionate	200 mg/1 mL
446	Testosterone Cypionate	Injection	Testosterone Cypionate	200 mg/1 mL
447	Testosterone Cypionate	Injection	Testosterone Cypionate	200 mg/1 mL
448	Testosterone Cypionate	Injection	Testosterone Cypionate	200 mg/1 mg
449	Testosterone Cypionate	Injection	Testosterone Cypionate	200 mg/1 mg
450	Testosterone Cypionate	Injection	Testosterone Cypionate	200 mg/1 mg
451	Testosterone Cypionate	Injection	Testosterone Cypionate	200 mg/200 mg
452	Testosterone Cypionate	Injection	Testosterone Cypionate	50 mg/1 mL
453	Testosterone Cypionate	Injection	Testosterone Enanthate; Testosterone Cypionate; Nandrolone Decanoate	70 mg/1 mL; 70 mg/1 mL; 60 mg/1 mL
454	Testosterone Propionate	Cream	Testosterone Propionate	100 mg/6 mL
455	Testosterone Propionate	Cream	Testosterone Propionate	20 mg/1 g
456	Testosterone Propionate	Cream	Testosterone Propionate	20 mg/1 g
457	Testosterone Propionate	Cream	Testosterone Propionate	20 mg/1 mL
458	Testosterone Propionate	Gel	Testosterone Propionate	
459	Testosterone Propionate	Injection	Testosterone Propionate	100 mg/1 mL
460	Testosterone Propionate	Injection	Testosterone Propionate	100 mg/mL
461	Testosterone Propionate	Ointment	Testosterone Propionate	0.02
462	Testosterone Propionate	Ointment	Testosterone Propionate	20 mg/1 g

[a] Under "Active Ingredient Present from Listing," for combination products, methyltestosterone and testosterone enanthate are categorized as testosterone, and 7-keto-dehydroepiandrosterone as dehydroepiandrosterone.

[b] Under "All Reported Active Ingredient Strengths," if field is blank, ingredient strengths and/or units were not reported.

NOTE: Resources included peer-reviewed literature on use of cBHT (e.g., IJPC, 2018), cBHT preparation adverse event reports (FDA, 2018, 2020), information provided by compounding practitioners (see Public Access Folder), recent biannual outsourcing facility preparation reports (FDA, 2019), and online marketing information from compounding pharmacies.

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Appendix G

Compounded Bioidentical Hormone Therapy Formulations with Two or More Active Ingredients

The table begins on the following page.

No.	Active Ingredients Present from Listing[a]	Dosage Form	All Reported Active Ingredients	All Reported Active Ingredient Strengths[b]
1	Dehydroepiandrosterone Pregnenolone	Capsule	Dehydroepiandrosterone Sodium Sulfate Anhydrous; Pregnenolone	15 mg; 75 mg
2	Dehydroepiandrosterone Pregnenolone	Suspension	Dehydroepiandrosterone Sodium Sulfate Anhydrous; Pregnenolone	16 mg/1 mL; 40 mg/1 mL
3	Dehydroepiandrosterone Testosterone	Cream	Testosterone; Dehydroepiandrosterone	20 mg/1 mL; 200 mg/1 mL
4	Dehydroepiandrosterone Testosterone	Gel	Dehydroepiandrosterone; Testosterone	15 mg/1 mL; 4 mg/1 mL
5	Dehydroepiandrosterone Testosterone	Lozenge	Testosterone; Dehydroepiandrosterone	2 mg; 15 mg
6	Estradiol Progesterone	Capsule	Estradiol; Progesterone	0.25 mg; 100 mg
7	Estradiol Progesterone	Cream	Estradiol; Progesterone	0.4 mg/1 mL; 40 mg/1 mL
8	Estradiol Progesterone	Cream	Estradiol; Progesterone	0.65 mg/1 mL; 125 mg/1 mL
9	Estradiol Progesterone	Cream	Estradiol; Progesterone	1.2 mg/1 mL; 150 mg/1 mL
10	Estradiol Progesterone	Cream	Estradiol; Progesterone	4.2 mg/1 mL; 200 mg/1 mL
11	Estradiol Estriol	Capsule	Estradiol; Estriol	0.09 mg; 0.36 mg
12	Estradiol Estriol	Capsule	Estradiol; Estriol	0.25 mg; 0.25 mg
13	Estradiol Estriol	Capsule	Estradiol; Estriol	0.25 mg; 1 mg
14	Estradiol Estriol	Capsule	Estradiol; Estriol	0.3 mg; 0.3 mg
15	Estradiol Estriol	Capsule	Estradiol; Estriol	0.5 mg; 0.5 mg
16	Estradiol Estriol	Capsule	Estradiol; Estriol	0.625 mg; 0.625 mg
17	Estradiol Estriol	Capsule	Estradiol; Estriol	0.75 mg; 3 mg
18	Estradiol Estriol	Capsule	Estriol; Estradiol	1.25 mg

19	Estradiol Estriol	Capsule	Bi-Estrogen Oral Capsule: (Estriol/Estradiol) 60/40 or 70/30 or 80/20	1.25 mg; 2.5 mg
20	Estradiol Estriol	Capsule	Estradiol; Estriol	1.5 mg; 1.5 mg
21	Estradiol Estriol	Capsule	Estriol; Estradiol	2.5 mg
22	Estradiol Estriol	Capsule	Estriol; Estradiol	5 mg
23	Estradiol Estriol	Cream	Bi-Est 50:50 (50% Estradiol, 50% Estriol) Cream	0.25 mg; 0.5 mg; 0.75 mg; 1 mg
24	Estradiol Estriol	Cream	Estradiol; Estriol	0.1 mg/0.5 g; 0.1 mg/0.5 g
25	Estradiol Estriol	Cream	Estradiol; Estriol	0.1 mg/0.5 g; 0.1 mg/0.5 g
26	Estradiol Estriol	Cream	Estradiol; Estriol	0.1 mg/0.5 g; 0.1 mg/0.5 g
27	Estradiol Estriol	Cream	Estradiol; Estriol	0.1 mg/1 mL; 0.4 mg/1 mL
28	Estradiol Estriol	Cream	Estradiol; Estriol	0.125 mg/1 mL; 0.5 mg/1 mL
29	Estradiol Estriol	Cream	Estradiol; Estriol	0.15 mg/0.5 g; 0.15 mg/0.5 g
30	Estradiol Estriol	Cream	Estradiol; Estriol	0.2 mg/1 mL; 0.8 mg/1 mL
31	Estradiol Estriol	Cream	Estradiol; Estriol	0.25 mg/1 mL; 0.25 mg/1 mL
32	Estradiol Estriol	Cream	Estradiol; Estriol	0.25 mg/1 mL; 1 mg/1 mL
33	Estradiol Estriol	Cream	Estradiol; Estriol	0.375 mg/1 mL; 0.375 mg/1 mL
34	Estradiol Estriol	Cream	Estradiol; Estriol	0.4 mg/1 g; 0.4 mg/1 g
35	Estradiol Estriol	Cream	Estradiol; Estriol	0.4 mg/1 mL; 0.4 mg/1 mL
36	Estradiol Estriol	Cream	Estradiol; Estriol	0.4 mg/1 mL; 1.6 mg/1 mL
37	Estradiol Estriol	Cream	Estradiol; Estriol	0.5 mg/1 g; 2 mg/1 g
38	Estradiol Estriol	Cream	Estradiol; Estriol	0.5 mg/1 g; 2 mg/1 g

continued

No.	Active Ingredients Present from Listing[a]	Dosage Form	All Reported Active Ingredients	All Reported Active Ingredient Strengths[b]
39	Estradiol Estriol	Cream	Estradiol; Estriol	0.5 mg/1 g; 2.5 mg/1 g
40	Estradiol Estriol	Cream	Estradiol; Estriol	0.5 mg/1 mL; 0.5 mg/1 mL
41	Estradiol Estriol	Cream	Estradiol; Estriol	0.5 mg/1 mL; 2 mg/1 mL
42	Estradiol Estriol	Cream	Estradiol; Estriol	0.6 mg/1 mL; 0.6 mg/1 mL
43	Estradiol Estriol	Cream	Estradiol; Estriol	0.8 mg/1 mL; 0.8 mg/1 mL
44	Estradiol Estriol	Cream	Estradiol; Estriol	0.8 mg/1 mL; 3.2 mg/1 mL
45	Estradiol Estriol	Cream	Estradiol; Estriol	1 mg/1 mL; 1 mg/1 mL
46	Estradiol Estriol	Cream	Estradiol; Estriol	1 mg/1 mL; 4 mg/1 mL
47	Estradiol Estriol	Cream	Estradiol; Estriol	1.2 mg/1 mL; 1.2 mg/1 mL
48	Estradiol Estriol	Cream	Estradiol; Estriol	1.25 mg/1 mL; 1.25 mg/1 mL
49	Estradiol Estriol	Cream	Bi-Estrogen Cream: (Estriol/ Estradiol) 50/50 or 60/40 or 70/30 or 80/20	1.25 mg/0.1 mL; 2.5 mg/0.1 mL
50	Estradiol Estriol	Cream	Estradiol; Estriol	1.5 mg/1 mL; 3.5 mg/1 mL
51	Estradiol Estriol	Cream	Estradiol; Estriol	2 mg/1 g; 3 mg/1 g
52	Estradiol Estriol	Cream	Estradiol; Estriol	2 mg/1 mL; 2 mg/1 mL
53	Estradiol Estriol	Cream	Estriol; Estradiol	2 mg/g; 0.5 mg/g
54	Estradiol Estriol	Cream	Estradiol; Estriol	2.5 mg/1 mL; 2.5 mg/1 mL
55	Estradiol Estriol	Cream	Estradiol; Estriol	3 mg/1 mL; 2 mg/1 mL
56	Estradiol Estriol	Cream	Estradiol; Estriol	5 mg/1 mL; 5 mg/1 mL
57	Estradiol Estriol	Cream	Estradiol; Estriol	6.25 mg/1 mL; 6.25 mg/1 mL
58	Estradiol Estriol	Gel	Estradiol; Estriol	1.25 mg/1 mL; 1.25 mg/1 mL

59	Estradiol Estriol	Gel	Estriol; Estradiol	2 mg/mL; 0.5 mg/mL
60	Estradiol Estriol	Lozenge	Estriol; Estradiol	0.3125 mg; 0.9375 mg
61	Estradiol Estriol	Lozenge	Estriol; Estradiol	0.5 mg; 0.125 mg
62	Estradiol Estriol	Lozenge	Estriol; Estradiol	0.6 mg; 0.15 mg
63	Estradiol Estriol	Ointment	Estradiol; Estriol	0.5 mg/1 g; 2 mg/1 g
64	Estradiol Estriol	Ointment	Estradiol; Estriol	0.5 mg/1 g; 2 mg/1 g
65	Estradiol Estriol	Ointment	Estradiol; Estriol	1 mg/1 g; 1.5 mg/1 g
66	Estradiol Estriol	Solution	Estradiol; Estriol	1.25 mg/1 mL; 1.25 mg/1 mL
67	Estradiol Estriol	Solution	Estradiol; Estriol	2 mg/1 mL; 8 mg/1 mL
68	Estradiol Estriol	Solution	Estriol; Estradiol	2 mg; 0.25 mg/mL
69	Estradiol Testosterone	Cream	Estradiol; Testosterone	0.3 mg/1 mL; 1 mg/1 mL
70	Estradiol Testosterone	Cream	Estradiol; Testosterone	0.3 mg/1 mL; 1 mg/1 mL
71	Estradiol Testosterone	Cream	Estradiol; Testosterone	0.4 mg/1 mL; 2 mg/1 mL
72	Estradiol Testosterone	Cream	Estradiol; Testosterone	0.5 mg/1 mL; 0.75 mg/1 mL
73	Estradiol Testosterone	Ointment	Estradiol; Testosterone	0.3 mg/1 g; 0.1 mg/1 g
74	Estradiol Testosterone	Ointment	Estradiol; Testosterone	0.3 mg/1 g; 1 mg/1 g
75	Estradiol Testosterone	Ointment	Estradiol; Testosterone	1 mg/1 g; 0.5 mg/1 g
76	Estriol Progesterone	Cream	Progesterone; Estriol	25 mg/1 g; 3 mg/1 g
77	Estriol Testosterone	Cream	Testosterone; Estriol	0.5 mg/1 g; 2 mg/1 g
78	Estriol Testosterone	Cream	Estriol; Testosterone	1 mg/1 g; 3 mg/1 g
79	Estriol Testosterone	Cream	Estriol; Testosterone	1 mg/1 g; 3 mg/1 g
80	Estriol Testosterone	Cream	Estriol; Testosterone; Desonide	10 mg/1 g; 2.5 mg/1 g; 0.5 mg/1 g
81	Estriol Testosterone	Cream	Testosterone; Estriol	4 mg/1 g; 6 mg/1 g

continued

No.	Active Ingredients Present from Listing[a]	Dosage Form	All Reported Active Ingredients	All Reported Active Ingredient Strengths[b]
82	Estriol Testosterone	Gel	Testosterone; Estriol	0.25 mg/1 g; 0.5 mg/1 g
83	Estriol Testosterone	Gel	Estriol; Testosterone	0.25 mg/1 mL; 2 mg/1 mL
84	Estriol Testosterone	Ointment	Lidocaine Hydrochloride; Testosterone; Estriol	50 mg/1 g; 0.5 mg/1 g; 2.5 mg/1 g
85	Estriol Testosterone	Suppository	Estriol; Testosterone	2 mg; 0.5 mg
86	Pregnenolone Progesterone	Cream	Progesterone; Pregnenolone	150 mg/1 mL; 5 mg/1 mL
87	Progesterone Testosterone	Capsule	Progesterone; Methyltestosterone	100 mg; 1.25 mg
88	Progesterone Testosterone	Cream	Testosterone; Progesterone	2 mg/1 g; 100 mg/1 g
89	Progesterone Testosterone	Cream	Testosterone; Progesterone	2 mg/1 g; 200 mg/1 g
90	Progesterone Testosterone	Cream	Testosterone; Progesterone	2 mg/1 g; 50 mg/1 g
91	Progesterone Testosterone	Cream	Progesterone; Testosterone	20 mg/0.5 g; 1.25 mg/0.5 g
92	Progesterone Testosterone	Cream	Progesterone; Testosterone	225 mg/1 mL; 0.5 mg/1 mL
93	Progesterone Testosterone	Cream	Progesterone; Testosterone	30 mg/1 mL; 0.25 mg/1 mL
94	Progesterone Testosterone	Cream	Progesterone; Testosterone	30 mg/1 mL; 2 mg/1 mL
95	Progesterone Testosterone	Cream	Testosterone; Progesterone	4 mg/1 g; 200 mg/1 g
96	Progesterone Testosterone	Cream	Testosterone; Progesterone	4 mg/1 g; 50 mg/1 g
97	Progesterone Testosterone	Cream	Testosterone; Progesterone	4 mg/1 g; 70 mg/1 g
98	Testosterone Cypionate; Testosterone Propionate	Injection	Testosterone Cypionate; Testosterone Propionate	160 mg/200 mg; 40 mg/200 mg
99	Testosterone Cypionate; Testosterone Propionate	Injection	Testosterone Propionate; Testosterone Cypionate	20 mg/1 mL; 200 mg/1 mL
100	Testosterone Cypionate; Testosterone Propionate	Injection	Testosterone Propionate; Testosterone Cypionate	20 mg/1 mL; 200 mg/1 mL

101	Dehydroepiandrosterone; Estradiol; Estriol	Cream	Estriol; Estradiol; 7-Keto-Dehydroepiandrosterone	1.25 mg/1 mL; 1.25 mg/1 mL; 20 mg/1 mL
102	Dehydroepiandrosterone; Estriol; Progesterone	Lozenge	Estriol; Progesterone; 7-Keto-Dehydroepiandrosterone	1 mg; 10 mg; 10 mg
103	Dehydroepiandrosterone; Estriol; Progesterone	Lozenge	Estriol; Progesterone; 7-Keto-Dehydroepiandrosterone	1 mg; 15 mg; 10 mg
104	Dehydroepiandrosterone; Pregnenolone; Progesterone	Capsule	Progesterone; Dehydroepiandrosterone Sodium Sulfate Anhydrous; Pregnenolone	100 mg; 10 mg; 10 mg
105	Dehydroepiandrosterone; Pregnenolone; Progesterone	Cream	Progesterone; Pregnenolone; Dehydroepiandrosterone	125 mg/1 mL; 10 mg/1 mL; 10 mg/1 mL
106	Dehydroepiandrosterone; Pregnenolone; Progesterone	Cream	Dehydroepiandrosterone; Progesterone; Pregnenolone	5 mg/1 mL; 100 mg/1 mL; 10 mg/1 mL
107	Dehydroepiandrosterone; Progesterone Testosterone	Cream	7-Keto-Dehydroepiandrosterone; Testosterone; Progesterone	2 mg/1 g; 1 mg/1 g; 160 mg/1 g
108	Estradiol; Progesterone; Testosterone	Capsule	Progesterone; Estradiol, Testosterone	
109	Estradiol; Progesterone; Testosterone	Capsule	Estradiol; Methyltestosterone; Progesterone	0.85 mg; 1.5 mg; 175 mg
110	Estradiol; Progesterone; Testosterone	Capsule	Estradiol; Progesterone; Methyltestosterone	1.1 mg; 165 mg; 1 mg
111	Estradiol; Progesterone; Testosterone	Capsule	Estradiol; Methyltestosterone; Progesterone	1.3 mg; 2.75 mg; 160 mg
112	Estradiol; Progesterone; Testosterone	Capsule	Estradiol; Methyltestosterone; Progesterone	1.9 mg; 1 mg; 170 mg
113	Estradiol; Progesterone; Testosterone	Cream	Estradiol; Testosterone; Progesterone	0.4 mg/1 mL; 2.2 mg/1 mL; 85 mg/1 mL

continued

No.	Active Ingredients Present from Listing[a]	Dosage Form	All Reported Active Ingredients	All Reported Active Ingredient Strengths[b]
114	Estradiol; Progesterone; Testosterone	Cream	Estradiol; Testosterone; Progesterone	0.55 mg/1 mL; 1.5 mg/1 mL; 95 mg/1 mL
115	Estradiol; Progesterone; Testosterone	Cream	Estradiol; Testosterone; Progesterone	0.65 mg/1 mL; 1.5 mg/1 mL; 125 mg/1 mL
116	Estradiol; Progesterone; Testosterone	Cream	Estradiol; Testosterone; Progesterone	0.7 mg/1 mL; 1.5 mg/1 mL; 135 mg/1 mL
117	Estradiol; Progesterone; Testosterone	Cream	Estradiol; Testosterone; Progesterone	2 mg/1 mL; 0.5 mg/1 mL; 125 mg/1 mL
118	Estradiol Estriol; Estrone	Capsule	Estradiol; Estriol; Estrone	0.25 mg; 2 mg; 0.25 mg
119	Estradiol Estriol; Estrone	Capsule	Estradiol; Estriol; Estrone	2.5 mg
120	Estradiol Estriol; Estrone	Capsule	Estradiol; Estriol; Estrone	2.5 mg
121	Estradiol Estriol; Estrone	Capsule	Estradiol; Estriol; Estrone	2.5 mg
122	Estradiol Estriol; Estrone	Capsule	Estradiol; Estriol; Estrone	2.5 mg
123	Estradiol Estriol; Estrone	Capsule	Estradiol; Estriol; Estrone	2.5 mg
124	Estradiol Estriol; Estrone	Cream	Estradiol; Estriol; Estrone	0.25 mg/g; 2 mg/g; 0.25 mg/g
125	Estradiol Estriol; Estrone	Cream	Estriol; Estradiol; Estrone	10 mg/1 mL; 1.25 mg/1 mL; 1.25 mg/1 mL
126	Estradiol Estriol; Estrone	Gel	Estradiol; Estriol; Estrone	2.5 mg/0.1 mL
127	Estradiol Estriol; Estrone	Injection	Estradiol; Estriol; Estrone	2.5 mg/mL
128	Estradiol Estriol; Estrone	Solution	Estradiol; Estriol; Estrone	0.25 mg/mL; 2 mg/mL; 0.25 mg/mL
129	Estradiol Estriol; Estrone	Solution	Estradiol; Estriol; Estrone	2.5 mg/0.1 mL
130	Estradiol Estriol; Estrone	Tablet	Estradiol; Estriol; Estrone	2.5 mg
131	Estradiol Estriol; Progesterone	Capsule	Estradiol; Progesterone; Estriol	0.05 mg; 125 mg; 0.45 mg

132	Estradiol Estriol; Progesterone	Capsule	Estradiol; Progesterone; Estriol	0.06 mg; 100 mg; 0.24 mg
133	Estradiol Estriol; Progesterone	Capsule	Estradiol; Progesterone; Estriol	0.06 mg; 125 mg; 0.24 mg
134	Estradiol Estriol; Progesterone	Capsule	Estradiol; Progesterone; Estriol	0.08 mg; 100 mg; 0.32 mg
135	Estradiol Estriol; Progesterone	Capsule	Estradiol; Progesterone; Estriol	0.1 mg; 100 mg; 0.1 mg
136	Estradiol Estriol; Progesterone	Capsule	Estradiol; Progesterone; Estriol	0.1 mg; 70 mg; 0.4 mg
137	Estradiol Estriol; Progesterone	Capsule	Estradiol; Progesterone; Estriol	0.12 mg; 50 mg; 0.28 mg
138	Estradiol Estriol; Progesterone	Capsule	Estradiol; Progesterone; Estriol	0.15 mg; 80 mg; 0.15 mg
139	Estradiol Estriol; Progesterone	Capsule	Estradiol; Progesterone; Estriol	0.16 mg; 50 mg; 0.64 mg
140	Estradiol Estriol; Progesterone	Capsule	Estradiol; Progesterone; Estriol	0.25 mg; 50 mg; 1 mg
141	Estradiol Estriol; Progesterone	Capsule	Estriol; Estradiol; Progesterone	0.32 mg; 0.08 mg; 125 mg
142	Estradiol Estriol; Progesterone	Capsule	Estradiol; Progesterone; Estriol	0.5 mg; 120 mg; 0.5 mg
143	Estradiol Estriol; Progesterone	Capsule	Estradiol; Progesterone; Estriol	0.5 mg; 125 mg; 0.5 mg
144	Estradiol Estriol; Progesterone	Capsule	Estradiol; Progesterone; Estriol	1.15 mg; 175 mg; 1.15 mg
145	Estradiol Estriol; Progesterone	Cream	Estradiol; Progesterone; Estriol	0.08 mg/1 mL; 10 mg/1 mL; 0.32 mg/1 mL

continued

No.	Active Ingredients Present from Listing[a]	Dosage Form	All Reported Active Ingredients	All Reported Active Ingredient Strengths[b]
146	Estradiol Estriol; Progesterone	Cream	Estradiol; Progesterone; Estriol	0.08 mg/1 mL; 30 mg/1 mL; 0.32 mg/1 mL
147	Estradiol Estriol; Progesterone	Cream	Estriol; Estradiol; Progesterone	0.1 mg/1 mL; 0.1 mg/1 mL; 40 mg/1 mL
148	Estradiol Estriol; Progesterone	Cream	Estriol; Estradiol; Progesterone	0.25 mg/1 mL; 0.25 mg/1 mL; 25 mg/1 mL
149	Estradiol Estriol; Progesterone	Cream	Estradiol; Progesterone; Estriol	0.25 mg/1 mL; 200 mg/1 mL; 0.25 mg/1 mL
150	Estradiol Estriol; Progesterone	Cream	Estradiol; Progesterone; Estriol	0.25 mg/1 mL; 25 mg/1 mL; 0.25 mg/1 mL
151	Estradiol Estriol; Progesterone	Cream	Estriol; Progesterone; Estradiol	0.5 mg/1 g; 200 mg/1 g; 0.5 mg/1 g
152	Estradiol Estriol; Progesterone	Cream	Estriol; Progesterone; Estradiol	0.5 mg/1 g; 200 mg/1 g; 0.5 mg/1 g
153	Estradiol Estriol; Progesterone	Cream	Estriol; Progesterone; Estradiol	0.5 mg/1 g; 40 mg/1 g; 0.5 mg/1 g
154	Estradiol Estriol; Progesterone	Cream	Estradiol; Progesterone; Estriol	0.5 mg/1 mL; 30 mg/1 mL; 0.5 mg/1 mL
155	Estradiol Estriol; Progesterone	Cream	Estriol; Progesterone; Estradiol	0.8 mg/1 g; 20 mg/1 g; 0.2 mg/1 g
156	Estradiol Estriol; Progesterone	Cream	Estriol, Estradiol; Progesterone	0.2%; 0.2%; 12.5%
157	Estradiol Estriol; Progesterone	Cream	Estriol; Progesterone; Estradiol	1 mg/1 g; 100 mg/1 g; 1 mg/1 g
158	Estradiol Estriol; Progesterone	Cream	Estriol; Progesterone; Estradiol	1 mg/1 g; 100 mg/1 g; 1 mg/1 g

159	Estradiol Estriol; Progesterone	Cream	Estriol; Progesterone; Estradiol	1 mg/1 g; 100 mg/1 g; 1 mg/1 g
160	Estradiol Estriol; Progesterone	Cream	Estriol; Progesterone; Estradiol	1 mg/1 g; 200 mg/1 g; 1 mg/1 g
161	Estradiol Estriol; Progesterone	Cream	Estriol; Progesterone; Estradiol	1 mg/1 g; 40 mg/1 g; 0.25 mg/1 g
162	Estradiol Estriol; Progesterone	Cream	Estriol; Progesterone; Estradiol	1 mg/1 g; 50 mg/1 g; 1 mg/1 g
163	Estradiol Estriol; Progesterone	Cream	Estriol; Estradiol; Progesterone	1 mg/1 mL; 0.25 mg/1 mL; 100 mg/1 mL
164	Estradiol Estriol; Progesterone	Cream	Estriol; Progesterone; Estradiol	2 mg/1 g; 160 mg/1 g; 2 mg/1 g
165	Estradiol Estriol; Progesterone	Cream	Estradiol; Progesterone; Estriol	2.5 mg/1 mL; 50 mg/1 mL; 2.5 mg/1 mL
166	Estradiol Estriol; Progesterone	Cream	Progesterone; Estriol; Estradiol	20 mg/0.5 g; 0.1 mg/0.5 g; 0.1 mg/0.5 g
167	Estradiol Estriol; Progesterone	Cream	Progesterone; Estriol; Estradiol	20 mg/1 mL; 0.2 mg/1 mL; 0.05 mg/1 mL
168	Estradiol Estriol; Progesterone	Lozenge	Estradiol; Progesterone; Estriol	0.16 mg; 200 mg; 0.64 mg
169	Estradiol Estriol; Progesterone	Lozenge	Estradiol; Progesterone; Estriol	2.8 mg; 120 mg; 11.2 mg
170	Estradiol Estriol; Progesterone	Lozenge	Progesterone; Estriol; Estradiol	25 mg; 2.4 mg; 0.6 mg
171	Estradiol Estriol; Progesterone	Lozenge	Progesterone; Estriol; Estradiol	30 mg; 1.6 mg; 0.4 mg
172	Estradiol Estriol; Progesterone	Lozenge	Progesterone; Estriol; Estradiol	30 mg; 2 mg; 0.5 mg

continued

No.	Active Ingredients Present from Listing[a]	Dosage Form	All Reported Active Ingredients	All Reported Active Ingredient Strengths[b]
173	Estradiol Estriol; Testosterone	Cream	Estriol; Estradiol; Testosterone	0.2 mg/0.5 g; 0.2 mg/0.5 g; 1 mg/0.5 g
174	Estradiol Estriol; Testosterone	Cream	Estriol; Estradiol; Testosterone	0.25 mg/1 mL; 0.25 mg/1 mL; 2 mg/1 mL
175	Estradiol Estriol; Testosterone	Cream	Estradiol; Testosterone; Estriol	0.25 mg/1 mL; 0.5 mg/1 mL; 1 mg/1 mL
176	Estradiol Estriol; Testosterone	Cream	Estradiol; Testosterone; Estriol	0.3 mg/1 mL; 1 mg/1 mL; 1.2 mg/1 mL
177	Estradiol Estriol; Testosterone	Cream	Estradiol; Testosterone; Estriol	0.5 mg/1 mL; 0.5 mg/1 mL; 0.5 mg/1 mL
178	Estradiol Estriol; Testosterone	Cream	Estradiol; Testosterone; Estriol	0.5 mg/1 mL; 1 mg/1 mL; 0.5 mg/1 mL
179	Estradiol Estriol; Testosterone	Cream	Estradiol; Testosterone; Estriol	0.5 mg/1 mL; 1.5 mg/1 mL; 0.5 mg/1 mL
180	Estradiol Estriol; Testosterone	Cream	Estriol; Estradiol; Testosterone	1 mg/1 g; 1 mg/1 g; 2 mg/1 g
181	Estradiol Estriol; Testosterone	Cream	Estriol; Estradiol; Testosterone	1 mg/1 g; 1 mg/1 g; 4 mg/1 g
182	Estradiol Estriol; Testosterone	Cream	Estradiol; Testosterone; Estriol	1 mg/1 mL; 1 mg/1 mL; 1 mg/1 mL
183	Estradiol Estriol; Testosterone	Cream	Estradiol; Testosterone; Estriol	1 mg/1 mL; 3 mg/1 mL; 1 mg/1 mL
184	Estradiol Estriol; Testosterone	Cream	Estradiol; Testosterone; Estriol	2 mg/1 mL; 1 mg/1 mL; 8 mg/1 mL
185	Estradiol Estriol; Testosterone	Cream	Estradiol; Testosterone; Estriol	2 mg/1 mL; 1.5 mg/1 mL; 2 mg/1 mL

186	Estradiol Estriol; Testosterone	Cream	Estradiol; Testosterone; Estriol	3 mg/1 mL; 4 mg/1 mL; 3 mg/1 mL
187	Estradiol Estriol; Testosterone	Cream	Estradiol; Testosterone; Estriol	3.75 mg/1 mL; 2.5 mg/1 mL; 3.75 mg/1 mL
188	Estradiol Estriol; Testosterone	Cream	Estradiol; Testosterone; Estriol	4 mg/1 mL; 6 mg/1 mL; 4 mg/1 mL
189	Estradiol Estriol; Testosterone	Cream	Estradiol; Testosterone; Estriol	5 mg/1 mL; 2.5 mg/1 mL; 5 mg/1 mL
190	Estriol; Progesterone; Testosterone	Cream	Testosterone; Estriol; Progesterone	4 mg/1 g; 6 mg/1 g; 100 mg/1 g
191	Dehydroepiandrosterone; Estradiol; Progesterone; Testosterone	Capsule	Estradiol; Methyltestosterone; Progesterone; Dehydroepiandrosterone	0.75 mg; 1.5 mg; 150 mg; 7.5 mg
192	Dehydroepiandrosterone; Estradiol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Dehydroepiandrosterone	0.35 mg/1 mL; 150 mg/1 mL; 1.9 mg/ 1 mL; 7 mg/1 mL
193	Dehydroepiandrosterone; Estradiol; Estriol; Progesterone	Capsule	Estradiol; Progesterone; Dehydroepiandrosterone; Estriol	0.85 mg; 95 mg; 5 mg; 0.35 mg
194	Dehydroepiandrosterone; Estradiol; Estriol; Progesterone	Cream	Estriol; Estradiol; Progesterone; 7-Keto-Dehydroepiandrosterone	0.05 mg/1 mL; 0.05 mg/1 mL; 15 mg/ 1 mL; 6 mg/1 mL
195	Dehydroepiandrosterone; Estradiol; Estriol; Progesterone	Cream	Estradiol; Progesterone; Dehydroepiandrosterone; Estriol	0.12 mg/1 mL; 40 mg/1 mL; 2 mg/1 mL; 0.48 mg/1 mL
196	Dehydroepiandrosterone; Estradiol; Estriol; Progesterone	Cream	Estriol; Estradiol; 7-Keto-Dehydroepiandrosterone; Progesterone	0.7 mg/1 mL; 0.3 mg/1 mL; 5 mg/1 mL; 40 mg/1 mL

continued

No.	Active Ingredients Present from Listing[a]	Dosage Form	All Reported Active Ingredients	All Reported Active Ingredient Strengths[b]
197	Dehydroepiandrosterone; Estradiol; Estriol; Testosterone	Cream	Estradiol; Testosterone; Estriol; Dehydroepiandrosterone	0.225 mg/1 mL; 1.5 mg/1 mL; 0.225 mg/1 mL; 5 mg/1 mL
198	Dehydroepiandrosterone; Estradiol; Estriol; Testosterone	Cream	Estradiol; Testosterone; Estriol; Dehydroepiandrosterone	0.225 mg/1 mL; 3 mg/1 mL; 0.225 mg/1 mL; 5 mg/1 mL
199	Dehydroepiandrosterone; Estradiol; Estriol; Testosterone	Cream	Estriol; Estradiol; Testosterone; 7-Keto-Dehydroepiandrosterone	1.25 mg/1 mL; 1.25 mg/1 mL; 4 mg/1 mL; 20 mg/1 mL
200	Estradiol Estriol; Estrone; Progesterone	Capsule	Estradiol; Progesterone; Estriol; Estrone	0.125 mg; 50 mg; 1 mg; 0.125 mg
201	Estradiol Estriol; Progesterone; Testosterone	Capsule	Estradiol; Progesterone; Testosterone; Estriol	0.1 mg; 150 mg; 2 mg; 0.4 mg
202	Estradiol Estriol; Progesterone; Testosterone	Capsule	Estriol; Estradiol; Progesterone; Testosterone	2.5 mg; 50 mg; 1 mg
203	Estradiol Estriol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Estriol	0.02 mg/1 mL; 125 mg/1 mL; 2 mg/1 mL; 0.08 mg/1 mL
204	Estradiol Estriol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Estriol	0.08 mg/1 mL; 20 mg/1 mL; 1 mg/1 mL; 0.32 mg/1 mL
205	Estradiol Estriol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Estriol	0.15 mg/1 mL; 100 mg/1 mL; 4 mg/1 mL; 0.35 mg/1 mL
206	Estradiol Estriol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Estriol	0.2 mg/1 mL; 150 mg/1 mL; 0.5 mg/1 mL; 0.8 mg/1 mL
207	Estradiol Estriol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Estriol	0.2 mg/1 mL; 30 mg/1 mL; 0.5 mg/1 mL; 0.3 mg/1 mL
208	Estradiol Estriol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Estriol	0.25 mg/1 mL; 30 mg/1 mL; 1 mg/1 mL; 0.25 mg/1 mL

209	Estradiol Estriol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Estriol	0.3 mg/1 mL; 25 mg/1 mL; 0.25 mg/1 mL; 1 mg/1 mL
210	Estradiol Estriol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Estriol	0.3 mg/1 mL; 40 mg/1 mL; 1 mg/1 mL; 0.3 mg/1 mL
211	Estradiol Estriol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Estriol	0.4 mg/1 mL; 200 mg/1 mL; 0.5 mg/1 mL; 1.6 mg/1 mL
212	Estradiol Estriol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Estriol	0.4 mg/1 mL; 200 mg/1 mL; 2 mg/1 mL; 1.6 mg/1 mL
213	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	0.5 mg/1 g; 0.5 mg/1 g; 100 mg/1 g; 1 mg/1 g
214	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	0.5 mg/1 g; 0.5 mg/1 g; 100 mg/1 g; 2 mg/1 g
215	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	0.5 mg/1 g; 0.5 mg/1 g; 100 mg/1 g; 2 mg/1 g
216	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	0.5 mg/1 g; 0.5 mg/1 g; 150 mg/1 g; 2 mg/1 g
217	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	0.5 mg/1 g; 0.5 mg/1 g; 200 mg/1 g; 2 mg/1 g
218	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	0.5 mg/1 g; 0.5 mg/1 g; 200 mg/1 g; 2 mg/1 g
219	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	0.5 mg/1 g; 0.5 mg/1 g; 50 mg/1 g; 2 mg/1 g
220	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	0.5 mg/1 g; 0.5 mg/1 g; 80 mg/1 g; 3 mg/1 g
221	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Testosterone; Progesterone	0.5 mg/1 mL; 0.5 mg/1 mL; 0.5 mg/1 mL; 60 mg/1 mL
222	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Testosterone; Progesterone	0.5 mg/1 mL; 0.5 mg/1 mL; 0.5 mg/1 mL; 60 mg/1 mL

continued

No.	Active Ingredients Present from Listing[a]	Dosage Form	All Reported Active Ingredients	All Reported Active Ingredient Strengths[b]
223	Estradiol Estriol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Estriol	0.5 mg/1 mL; 100 mg/1 mL; 1 mg/1 mL; 2 mg/1 mL
224	Estradiol Estriol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Estriol	0.5 mg/1 mL; 20 mg/1 mL; 0.5 mg/1 mL; 0.5 mg/1 mL
225	Estradiol Estriol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Estriol	0.5 mg/1 mL; 20 mg/1 mL; 1 mg/1 mL; 0.5 mg/1 mL
226	Estradiol Estriol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Estriol	0.6 mg/1 mL; 100 mg/1 mL; 1 mg/1 mL; 2.4 mg/1 mL
227	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	0.8 mg/1 g; 0.2 mg/1 g; 50 mg/1 g; 1 mg/1 g
228	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	0.875 mg/1 g; 0.875 mg/1 g; 50 mg/1 g; 5 mg/1 g
229	Estradiol Estriol; Progesterone; Testosterone	Cream	Testosterone; Estriol; Estradiol; Progesterone	1 mg/1 g; 0.5 mg/1 g; 0.5 mg/1 g; 60 mg/1 g
230	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	1 mg/1 g; 1 mg/1 g; 100 mg/1 g; 1 mg/1 g
231	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	1 mg/1 g; 1 mg/1 g; 100 mg/1 g; 1 mg/1 g
232	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	1 mg/1 g; 1 mg/1 g; 100 mg/1 g; 2 mg/1 g
233	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	1 mg/1 g; 1 mg/1 g; 100 mg/1 g; 2 mg/1 g
234	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	1 mg/1 g; 1 mg/1 g; 100 mg/1 g; 2 mg/1 g
235	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	1 mg/1 g; 1 mg/1 g; 150 mg/1 g; 1 mg/1 g

236	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	1 mg/1 g; 1 mg/1 g; 150 mg/1 g; 2 mg/1 g
237	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	1 mg/1 g; 1 mg/1 g; 150 mg/1 g; 2 mg/1 g
238	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	1 mg/1 g; 1 mg/1 g; 150 mg/1 g; 2 mg/1 g
239	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	1 mg/1 g; 1 mg/1 g; 200 mg/1 g; 2 mg/1 g
240	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	1 mg/1 g; 1 mg/1 g; 50 mg/1 g; 1 mg/1 g
241	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	1 mg/1 g; 1 mg/1 g; 60 mg/1 g; 2 mg/1 g
242	Estradiol Estriol; Progesterone; Testosterone	Cream	Testosterone; Estradiol; Progesterone; Estriol	1 mg/1 mL; 0.2 mg/1 mL; 30 mg/1 mL; 0.2 mg/1 mL
243	Estradiol Estriol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Estriol	1 mg/1 mL; 50 mg/1 mL; 4 mg/1 mL; 1 mg/1 mL
244	Estradiol Estriol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Estriol	1 mg/1 mL; 50 mg/1 mL; 8 mg/1 mL; 1 mg/1 mL
245	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	2 mg/1 g; 2 mg/1 g; 120 mg/1 g; 4 mg/1 g
246	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	2 mg/1 g; 2 mg/1 g; 200 mg/1 g; 2 mg/1 g
247	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone	2 mg/1 g; 2 mg/1 g; 50 mg/1 g; 4 mg/1 g
248	Estradiol Estriol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Estriol	2 mg/1 mL; 120 mg/1 mL; 2 mg/1 mL; 2 mg/1 mL
249	Estradiol Estriol; Progesterone; Testosterone	Cream	Progesterone; Estriol; Estradiol; Testosterone	20 mg/0.5 g; 0.1 mg/0.5 g; 0.1 mg/0.5 g; 2 mg/0.5 g

continued

No.	Active Ingredients Present from Listing[a]	Dosage Form	All Reported Active Ingredients	All Reported Active Ingredient Strengths[b]
250	Estradiol Estriol; Progesterone; Testosterone	Cream	Progesterone; Estriol; Estradiol; Testosterone	20 mg/0.5 g; 0.15 mg/0.5 g; 0.15 mg/0.5 g; 2 mg/0.5 g
251	Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Testosterone; Progesterone	3 mg/1 mL; 1 mg/1 mL; 1 mg/1 mL; 25 mg/1 mL
252	Estradiol Estriol; Progesterone; Testosterone	Cream	Progesterone; Estriol; Estradiol; Testosterone	35 mg/0.5 g; 0.25 mg/0.5 g; 0.25 mg/0.5 g; 2 mg/0.5 g
253	Estradiol Estriol; Progesterone; Testosterone	Cream	Progesterone; Estriol; Estradiol; Testosterone	50 mg/0.5 g; 0.3 mg/0.5 g; 0.3 mg/0.5 g; 1.5 mg/0.5 g
254	Estradiol Estriol; Progesterone; Testosterone	Cream	Progesterone; Estriol; Estradiol; Testosterone	80 mg/0.5 g; 0.25 mg/0.5 g; 0.25 mg/0.5 g; 0.25 mg/0.5 g
255	Estradiol Estriol; Progesterone; Testosterone	Solution	Estradiol; Progesterone; Testosterone; Estriol	0.5 mg/1 mL; 100 mg/1 mL; 2 mg/1 mL; 2 mg/1 mL
256	Estradiol Estriol; Pregnenolone; Progesterone	Cream	Estriol; Estradiol; Progesterone; Pregnenolone	2 mg/1 g; 2 mg/1 g; 40 mg/1 g; 50 mg/1 g
257	Dehydroepiandrosterone; Estradiol Estriol; Progesterone; Testosterone	Capsule	Estriol; Estradiol; Dehydroepiandrosterone; Methyltestosterone; Progesterone	5.25 mg; 1.5 mg; 5 mg; 4 mg; 190 mg
258	Dehydroepiandrosterone; Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Dehydroepiandrosterone; Estradiol; Progesterone; Testosterone	0.14 mg/1 mL; 4 mg/1 mL; 0.06 mg/1 mL; 40 mg/1 mL; 1 mg/1 mL
259	Dehydroepiandrosterone; Estradiol Estriol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Estriol; Dehydroepiandrosterone	0.15 mg/1 mL; 20 mg/1 mL; 4 mg/1 mL; 0.15 mg/1 mL; 10 mg/1 mL
260	Dehydroepiandrosterone; Estradiol Estriol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Estriol; Dehydroepiandrosterone	0.35 mg/1 mL; 85 mg/1 mL; 0.35 mg/1 mL; 0.35 mg/1 mL; 5 mg/1 mL

261	Dehydroepiandrosterone; Estradiol Estriol; Progesterone; Testosterone	Cream	Estriol; Estradiol; Progesterone; Testosterone; Dehydroepiandrosterone	0.75 mg/1 mL; 0.25 mg/1 mL; 20 mg/1 mL; 0.5 mg/1 mL; 5 mg/1 mL
262	Dehydroepiandrosterone; Estradiol Estriol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Dehydroepiandrosterone; Estriol	3.75 mg/1 mL; 75 mg/1 mL; 2 mg/1 mL; 10 mg/1 mL; 2.5 mg/1 mL
263	Dehydroepiandrosterone; Estradiol Estriol; Progesterone; Testosterone	Cream	Estradiol; Progesterone; Testosterone; Estriol; Dehydroepiandrosterone	4 mg/1 mL; 75 mg/1 mL; 2.5 mg/1 mL; 3 mg/1 mL; 15 mg/1 mL
264	Dehydroepiandrosterone; Estradiol Estriol; Progesterone; Testosterone	Gel	Estriol; Dehydroepiandrosterone; Estradiol; Progesterone; Testosterone	3 mg/1 mL; 30 mg/1 mL; 1.2 mg/1 mL; 50 mg/1 mL; 2 mg/1 mL
265	Estradiol Estriol; Estrone Progesterone; Testosterone	Capsule	Estradiol; Estriol; Estrone; Progesterone; Testosterone	2.5 mg; 100 mg; 1 mg
266	Estradiol Estriol; Estrone Progesterone; Testosterone	Cream	Estradiol; Estriol; Estrone; Progesterone; Testosterone	

[a] Under "Active Ingredient Present from Listing" for combination products, methyltestosterone and testosterone enanthate are categorized as testosterone, and 7-keto-dehydroepiandrosterone as dehydroepiandrosterone.

[b] Under "All Reported Active Ingredient Strengths," if field is blank, ingredient strengths and/or units were not reported.

NOTE: Resources included peer-reviewed literature on use of cBHT (e.g., IJPC, 2018), cBHT preparation adverse event reports (FDA, 2018, 2020), information provided by compounding practitioners (see Public Access Folder), recent biannual outsourcing facility preparation reports (FDA, 2019), and online marketing information from compounding pharmacies.

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Appendix H

Boxed Warnings on U.S. Food and Drug Administration–Approved Estrogen and Testosterone Products

All U.S. Food and Drug Administration (FDA)-approved estrogen-containing products (Stefanick, 2005) and topical testosterone products (FDA, 2015) must contain a boxed warning that provides the prescriber and patient with safety warnings for the most serious adverse events associated with the use of these products. See Figures H-1 and H-2 for the boxed warning for FDA-approved estrogen-containing and topical testosterone products, respectively.

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, PROBABLE DEMENTIA and BREAST CANCER

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Use adequate diagnostic measures, including directed or random endometrial sampling, when indicated, to rule out malignancy in postmenopausal women with undiagnosed, persistent or recurring abnormal genital bleeding *[see Warnings and Precautions (5.2)]*.

Cardiovascular Disorders and Probable Dementia

Do not use estrogen-alone therapy for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.4, 14.5)]*.

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo *[see Warnings and Precautions (5.1), and Clinical Studies (14.4)]*.

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.5)]*.

Only daily oral 0.625 mg CE was studied in the estrogen-alone substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events and dementia to lower CE doses, other routes of administration, or other estrogen-alone products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen-alone therapy, taking into account her individual risk profile.

Prescribe 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.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Do not use estrogen plus progestin therapy for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.4, 14.5)]*. The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo *[see Warnings and Precautions (5.1), and Clinical Studies (14.4)]*.

The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.5)]*.

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer *[see Warnings and Precautions (5.2), and Clinical Studies (14.4)]*.

Only daily oral 0.625 mg CE and 2.5 mg MPA were studied in the estrogen plus progestin substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events, dementia and breast cancer to lower CE plus other MPA doses, other routes of administration, or other estrogen plus progestin products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen plus progestin therapy, taking into account her individual risk profile.

Prescribe 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.

FIGURE H-1 Boxed warning included with FDA-approved estrogen-containing products.
SOURCE: NLM, 2020a.

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

- **Virilization has been reported in children who were secondarily exposed to testosterone gel *[see Warnings and Precautions (5.2) and Adverse Reactions (6.2)]*.**
- **Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel *[see Dosage and Administration (2.2) and Warnings and Precautions (5.2)]*.**
- **Healthcare providers should advise patients to strictly adhere to recommended instructions for use *[see Dosage and Administration (2.2), Warnings and Precautions (5.2) and Patient Counseling Information (17)]*.**

FIGURE H-2 Boxed warning included with FDA-approved topical testosterone products.
SOURCE: NLM, 2020b.

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