The Panel Put Policy-Making Before Patient Need

An Independent Analysis of the FDA-Commissioned NASEM Report, The Clinical Utility of Compounded Bioidentical Hormone Therapy: A Review of Safety, Effectiveness, and Use

APRIL 2021

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Introduction

In the United States, the Food and Drug Administration ("FDA") oversees the approval, marketing, and labeling of prescription drugs. However, it is the ***right*** and the ***duty*** of the ***physician*** to prescribe what he or she thinks is best for the patient. In its Code of Medical Ethics, the American Medical Association (AMA) states:[1]

> "The practice of medicine, and its embodiment in the clinical encounter between a patient and a physician, is **fundamentally a moral activity that arises from the imperative to care for patients and to alleviate suffering.** The relationship between a patient and a physician is based on trust, which gives rise to physicians' ethical responsibility to place patients' welfare above the physicians' own self-interest or obligations to others, to use sound medical judgment on patients' behalf, and to advocate for their patients' welfare."

Consistent with this principle, U.S. law prohibits the invasion of the FDA into the purview of the physician, as the FDA is not purposed to regulate the practice of medicine or to otherwise interfere with a doctor's care of a patient.[2] It is well-recognized that flexibility and respect for physicians' autonomy in caring for patients is "crucial for [doctors] to be able to judge what is best for each individual patient and to provide effective medical care of the highest quality."[3] Indeed, as recently as November 2020, the AMA "confirm[ed] its strong support for the autonomous clinical decision-making authority of a physician," and reaffirmed that it "strongly opposes the FDA's intrusion into the practice of medicine by making decisions for individual care."[4]

Despite its mandate to respect prescribers' autonomy, the FDA recently commissioned a report setting forth recommendations that constitute an intrusion into a physician's ability to practice medicine and to meet his or her patient's needs. On July 1, 2020, the National Academies of Sciences, Engineering, and Medicine ("NASEM") published *The Clinical Utility of Compounded Bioidentical Hormone Therapy: A Review of Safety, Efficacy, and Use* (the "NASEM Report" or the "Report"), wherein NASEM received a directive from the FDA to "assess the clinical utility" of treating patients with compounded bioidentical hormone therapy ("cBHT").[5] Specifically, the FDA commissioned NASEM to "review the uses of cBHT preparations and the available evidence that would support marketing claims of the safety and effectiveness of cBHT preparations."[6] The committee was also asked to identify patient populations that might benefit from using cBHT and to "[d]escribe the physical and chemical characteristics of compounded BHRT drug products."[7] The NASEM Report ultimately offered

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1 Patient-Physician Relationships: Code of Medical Ethics Opinion 1.1.1., American Medical Association, *available at* www.ama-assn.org/delivering-care/ethics/patient-physician-relationships (last accessed Apr. 2, 2021) (emphasis added).

2 21 U.S.C. § 396.

3 Wendy Teo. FDA and the Practice of Medicine. SETON HALL LEGISLATIVE JOURNAL. 2017;2(41):305, 309.

4 Handbook Addendum – Supplemental Business and Information, American Medical Association (Oct. 30, 2020), *available at* https://www.ama-assn.org/system/files/2020-10/nov20-handbook-addendum.pdf;W (last accessed Apr. 2, 2021).

5 PDF of NASEM Report (Online Version) p. 19.

6 PDF of NASEM Report (Online Version) pp. 18-19.

7 PDF of NASEM Report (Online Version) p. 19.

six recommendations which, if implemented, would severely restrict—or eliminate entirely—the ability of the physician to prescribe cBHT to his or her patients. NASEM's recommendations, discussed in more detail below, go beyond an assessment of "clinical utility," as demonstrated in its recommendation to review certain bioidentical hormones as candidates for the FDA Difficult to Compound List, discussed further below.[8]

The aim of this white paper is to compile a balanced analysis and unbiased view of issues concerning the cBHT market raised by FDA and in the NASEM Report. To that end, we evaluated whether the NASEM Report reflects an unbiased understanding of compounded hormone therapy and whether the recommendations set forth therein are well-supported by medical literature and clinical practice. The review of the NASEM Report included an independent analysis of the appropriateness of the overall study approach; the scope of the literature review and the studies selected for review; the composition of the NASEM committee; and the underlying assumptions and data upon which the recommendations were based.

Based upon our independent analysis, we conclude that the NASEM Report does not accurately or objectively reflect the available evidence on the effectiveness and safety of cBHT. We further conclude that the NASEM Report recommendations, if implemented, would harm patients across the U.S. and their prescribers' ability to care for them. As discussed below, there are more appropriate measures than NASEM's recommendations to ensure safe and appropriate use of cBHT.

We identified several areas for potential bias that likely influenced the recommendations offered by NASEM including, *inter alia*, the lack of practicing prescribers or pharmacists on the Study Committee; the lack of a single cBHT prescriber or compounding pharmacist on the Study Committee; and the affiliations of the Study Committee, including close ties to both the pharmaceutical industry and the FDA itself. We observed that NASEM ignored the body of evidence submitted by experienced prescribers and compounding pharmacists demonstrating that cBHT is both safe and effective—instead, it relied upon only thirteen of the hundreds[9] of studies submitted in preparing its recommendations. NASEM ignored the well-recognized and reasonable explanations as to why cBHT does not fit into the current regulatory framework for drug approvals— and instead seeks to hold compounded products to the same standards as FDA-approved drugs without consideration of the practical ramifications, or the applicable law and regulations that govern pharmaceutical compounding (*e.g.*, Federal Food, Drug and Cosmetic Act and the 2013 Drug Quality and Security Act). Further, NASEM ignored the existing clinical practices for ensuring patient safety and compliance.

As detailed throughout this white paper, cBHT is used for a variety of medically-necessary reasons by patients across the U.S., and continued access to cBHT is critical to patient health and well-being. Given the strong potential bias influencing the Committee's recommendations and the omission from the final report of key data supporting the safety and efficacy of cBHT, **we recommend that FDA not rely on or consider the NASEM Report.** It is further recommended that **FDA not take steps to limit access to cBHT without adequate evidence to support a risk to patients, which should be considered on a drug product and/or formulation basis.**

Instead of resolving concerns with appropriate cBHT use by eliminating or severely restricting use of cBHT drug products, FDA should work collaboratively with the medical and pharmacy compounding industries to improve upon and develop systems to address the perceived shortcomings in adverse event reporting and prescription labeling. Developing improved systems to provide patients information on use of ingredients commonly used in compounded therapies as well as improved systems for collecting adverse event information and safety reports will not only benefit the use of cBHT but will improve overall monitoring of compounded therapies.

8 PDF of NASEM Report (Online Version) p. 223.

9 *See* Report Release Webinar: Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy," NASEM (July 1, 2020), *available at* https://www.nationalacademies.org/event/07-01-2020/report-release-webinar-clinical-utility-of-treating-patients-with-compounded-bioidentical-hormone-replacement-therapy (timestamps 15:00 to 15:50) (last accessed Apr. 2, 2021).

Background

Brief Primer on Pharmaceutical Compounding

Pharmaceutical compounding is formally defined as "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."[10] Medications are compounded when a prescriber determines, **in his or her professional judgment**, that the use of a compounded preparation is **necessary**. Upon receipt of a valid prescription from a doctor, compounding pharmacies can prepare oral liquids, topical ointments, transdermal gels, suppositories, and other dosage forms that are not otherwise commercially available to meet specific patient needs.[11]

Compounding has been a "fundamental component of pharmacy practice and healthcare since ancient times."[12] In fact, compounding is considered to be the "origin of the practice of pharmacy."[13] In the U.S., the passage of the Food, Drug and Cosmetic Act of 1938 ("FD&C Act") granted the FDA the power to approve new pharmaceutical products.[14] Prior to this grant of power to the FDA in the early 20th century, virtually all medications were compounded because there were few, if any, commercially available products on the market.[15] Today, compounding is taught as part of the standard curriculum at most pharmacy schools,[16] and more than 32,000 pharmacies nationwide offer compounding services.[17]

Pharmacy compounding practice is subject to a myriad of federal and state regulations, as well as guidelines implemented by professional societies. At the federal level, Section 503A of the FD&C Act applies to compounding done by licensed physicians and licensed pharmacists who work in a state-licensed pharmacy or federal facility, legitimizing this pharmaceutical practice in law.[18] It mandates that a drug must be compounded by a licensed pharmacist and be based on the receipt of a valid prescription for an identified individual patient.[19] The bulk drug substances used in compounding must be accompanied by a valid certificate of analysis and be manufactured by an FDA-registered establishment.[20] Further, the bulk drug substances must comply with the United States Pharmacopeia ("USP") or National Formulary monograph, and the USP chapter on pharmacy compounding. In the case that such a monograph does not exist, those substances must be components of an FDA-approved drug product or appear on the FDA's list of bulk drug substances that can be used in compounding.[21] Pharmacists cannot compound with drug products that have been withdrawn or removed from the market as a result of FDA's determination that the drug product was unsafe or ineffective.[22]

Section 503B, which was added to the FD&C Act pursuant to the 2013 Drug Quality and Security Act ("DQSA"), applies to compounding done in outsourcing facilities by or under the supervision of a licensed pharmacist.[23] In addition to certain of the requirements set forth under Section 503A, Section 503B mandates that outsourcing facilities must adhere to current good manufacturing practice requirements ("CGMP").[24] 503B outsourcing facilities must submit adverse event reports to the FDA in accordance with specific content and format requirements, and must label the containers of compounded drugs with certain information.[25] Further, the FDA inspects outsourcing facilities according to a risk-based schedule.[26]

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10 <795> Pharmaceutical Compounding – Nonsterile Preparations, The United States Pharmacopeial Convention (2013) available at https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/gc795.pdf (last accessed Apr. 2, 2021).

11 American Pharmacists Association, Frequently Asked Questions About Pharmaceutical Compounding, *available at* https://www.pharmacist.com/frequently-asked-questions-about-pharmaceutical-compounding (last accessed Apr. 2, 2021).

12 Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients, Senate Hearing 108-378 (Oct. 23, 2003), *available at* https://www.govinfo.gov/content/pkg/CHRG-108shrg90129/html/CHRG-108shrg90129.htm (last accessed Apr. 2, 2021).

13 Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients, Senate Hearing 108-378 (Oct. 23, 2003), *available at* https://www.govinfo.gov/content/pkg/CHRG-108shrg90129/html/CHRG-108shrg90129.htm (last accessed Apr. 2, 2021).

14 Laws Enforced by FDA, FDA (Mar. 29, 2018), *available at* https://www.fda.gov/regulatory-information/laws-enforced-fda (last accessed Apr. 2, 2021).

15 Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients, Senate Hearing 108-378 (Oct. 23, 2003), *available at* https://www.govinfo.gov/content/pkg/CHRG-108shrg90129/html/CHRG-108shrg90129.htm (last accessed Apr. 2, 2021).

16 Thompson v. Western States Medical Center, 535 U.S. 357 (2002).

17 PDF of NASEM Report (Online Version) p. 37.

18 FD&C Act Provisions that Apply to Human Drug Compounding, FDA (Jul. 14, 2020) *available at* https://www.fda.gov/drugs/human-drug-compounding/fdc-act-provisions-apply-human-drug-compounding#:~:text=Section%20503A%20limits%20interstate%20distribution,providing%20for%20appropriate%20investigation%20of (last accessed Apr. 2, 2021).

19 FD&C Act Provisions that Apply to Human Drug Compounding, FDA (Jul. 14, 2020) *available at* https://www.fda.gov/drugs/human-drug-compounding/fdc-act-provisions-apply-human-drug-compounding#:~:text=Section%20503A%20limits%20interstate%20distribution,providing%20for%20appropriate%20investigation%20of (last accessed Apr. 2, 2021).

20 FD&C Act Provisions that Apply to Human Drug Compounding, FDA (Jul. 14, 2020) *available at* https://www.fda.gov/drugs/human-drug-compounding/fdc-act-provisions-apply-human-drug-compounding#:~:text=Section%20503A%20limits%20interstate%20distribution,providing%20for%20appropriate%20investigation%20of (last accessed Apr. 2, 2021).

21 FD&C Act Provisions that Apply to Human Drug Compounding, FDA (Jul. 14, 2020) *available at* https://www.fda.gov/drugs/human-drug-compounding/fdc-act-provisions-apply-human-drug-compounding#:~:text=Section%20503A%20limits%20interstate%20distribution,providing%20for%20appropriate%20investigation%20of (last accessed Apr. 2, 2021); Bulk Drug Substances Used in Compounding, FDA (Sep. 10, 2020) *available at* https://www.fda.gov/drugs/human-drug-compounding/bulk-drug-substances-used-compounding (last accessed Apr. 2, 2021).

22 FD&C Act Provisions that Apply to Human Drug Compounding, FDA (Jul. 14, 2020) *available at* https://www.fda.gov/drugs/human-drug-compounding/fdc-act-provisions-apply-human-drug-compounding#:~:text=Section%20503A%20limits%20interstate%20distribution,providing%20for%20appropriate%20investigation%20of (last accessed Apr. 2, 2021).

23 FD&C Act Provisions that Apply to Human Drug Compounding, FDA (Jul. 14, 2020) *available at* https://www.fda.gov/drugs/human-drug-compounding/fdc-act-provisions-apply-human-drug-compounding#:~:text=Section%20503A%20limits%20interstate%20distribution,providing%20for%20appropriate%20investigation%20of (last accessed Apr. 2, 2021).

24 FD&C Act Provisions that Apply to Human Drug Compounding, FDA (Jul. 14, 2020) *available at* https://www.fda.gov/drugs/human-drug-compounding/fdc-act-provisions-apply-human-drug-compounding#:~:text=Section%20503A%20limits%20interstate%20distribution,providing%20for%20appropriate%20investigation%20of (last accessed Apr. 2, 2021).

25 FD&C Act Provisions that Apply to Human Drug Compounding, FDA (Jul. 14, 2020) *available at* https://www.fda.gov/drugs/human-drug-compounding/fdc-act-provisions-apply-human-drug-compounding#:~:text=Section%20503A%20limits%20interstate%20distribution,providing%20for%20appropriate%20investigation%20of (last accessed Apr. 2, 2021).

26 Compounding Laws and Policies, FDA (Sep. 10, 2020) *available at* https://www.fda.gov/drugs/human-drug-compounding/compounding-laws-and-policies (last accessed Apr. 2, 2021).

At the state level, compounding practices are largely regulated by state legislatures and state boards of pharmacy. Although these rules differ by state, like other healthcare professions, most state boards of pharmacy require adherence to the USP standards for compounding. The USP develops standards for compounding medications to ensure patient benefit and to reduce risks, such as infection, contamination, or incorrect dosing.[27] Adherence to these standards by compounding pharmacies promotes patient safety by setting forth best practices for medication preparation. USP General Chapter <795> sets forth standards for good practices throughout the preparation of non-sterile compounded pharmaceutical formulations. It provides guidelines for minimizing the likelihood of cross-contamination or error during compounding.[28] Many pharmacies that compound non-sterile formulations "have been required to follow USP 795 requirements since 2000," and over the past two decades, the chapter has undergone multiple revisions to incorporate updated, evidence-based guidance.[29] In fact, these same standards are recognized in various provisions of the FD&C Act and are enforced by the FDA.[30] Additionally, as of 2016, at least 87% of boards of pharmacy either require full compliance with USP General Chapter <797> on Pharmaceutical Compounding of Sterile Preparations or incorporate USP General Chapter <797> into their state regulations in some way.[31] This chapter is intended to provide a set of standards for the safety and protection of both patients and healthcare workers involved in sterile compounding preparations "by reducing the potential for microbial contamination caused by an unclean environment and endotoxins."[32]

Compounding pharmacies also look to guidelines on compounding promulgated by national pharmacy organizations such as the National Association of Boards of Pharmacy ("NABP"), which publishes model rules for pharmacy state boards,[33] and the American Society of Health-System Pharmacists ("ASHP"), which publishes guidelines for use in hospitals including seven different guidance documents applicable to pharmaceutical compounding.[34] In addition, compounding pharmacies may seek accreditation for their compounding practices. For example, the Pharmacy Compounding Accreditation Board ("PCAB"), a service of the Accreditation Commission for Health Care ("ACHC"), grants accreditation to pharmacies that demonstrate compliance with national quality standards in compounding based on the USP guidelines.[35]

In sum, the practice of pharmaceutical compounding is a well-regulated and legitimate practice that remains a "vital element of healthcare" today.[36]

The Need for Compounded Bioidentical Hormone Therapy in the United States

The FDA recognizes that "compounding can serve an important patient need."[37] The need for compounded bioidentical hormone therapy ("cBHT") in the market is significant.

Hormones are essential for regulating major processes in the human body, such as metabolism, reproduction, and development. As such, a hormonal imbalance can influence a wide range of bodily functions and have a significant impact on a patient's quality of life.[38] To treat hormonal imbalances in their patients, physicians often supplement the hormones naturally produced in the body with those that are chemically and structurally identical, either through FDA-approved bioidentical hormone therapy ("BHT") products or cBHT.[39]

Bioidentical hormones are hormones that are chemically similar or structurally identical in molecular structure to hormones people make in their bodies, which means these hormones bind to receptors and act in the body similarly to hormones produced by the body.[40] This is a broad definition that includes FDA-approved hormone therapies and custom compounded products. Certain bioidentical hormones are commercially available by pharmaceutical manufacturers, such as micronized progesterone and estradiol.[41] However, other bioidentical hormones are prescribed by physicians in unique strengths and combinations, and these bioidentical hormone formulations are prepared in compounding pharmacies and are often referred to as cBHT.[42] Bioidentical hormones should not be confused with hormones that are referred to as "natural," such as Premarin, a conjugated estrogen made from horse urine, that is not structurally similar to human estrogen and has effects on the human body which are different than human estrogen, as discussed in more detail below.[43]

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27 USP General Chapter <795> Pharmaceutical Compounding – Nonsterile Preparations, USP, *available at* https://www.usp.org/compounding/general-chapter-795 (last accessed Apr. 2, 2021).

28 USP 797 and USP 795: Creating and managing a state of control, Wolters Kluwer (Apr. 7, 2016), *available at* https://www.wolterskluwer.com/en/expert-insights/usp-797-and-usp-795-creating-and-managing-a-state-of-control (last accessed Apr. 2, 2021).

29 Webinar: USP 795 compliance and best practices, Wolters Kluwer (Apr. 17, 2020), *available at* https://www.wolterskluwer.com/en/expert-insights/usp-795-compliance-and-best-practices?utm_landingPage=https://www.wolterskluwer.com/en/expert-insights/usp-797-and-usp-795-creating-and-managing-a-state-of-control&utm_prevPage=https://www.google.com/ (last accessed Apr. 2, 2021).

30 Recognition of USP Compounding Standards, USP, *available at* https://www.usp.org/compounding/legal-considerations (last accessed Apr. 2, 2021).

31 Recognition of USP Compounding Standards, USP, *available at* https://www.usp.org/compounding/legal-considerations (last accessed Apr. 2, 2021).

32 USP Chapter <797> Sterile Compounding Guidelines Overview, BD, *available at* https://www.bd.com/en-us/offerings/capabilities/syringes-and-needles/usp-general-chapter-797#:~:text=The%20purpose%20of%20USP%20Chapter,potential%20for%20microbial%20contamination%20caused (last accessed Apr. 2, 2021).

33 Model Pharmacy Act/Rules, NABP (2020), *available at* https://nabp.pharmacy/resources/model-pharmacy-act/ (last accessed Apr. 2, 2021).

34 The ASHP compounding guidelines are: *Minimum Standard for Pharmacies in Hospital, Minimum Standard for Pharmaceutical Services in Ambulatory Care, Technical Assistance Bulletin on Compounding Nonsterile Products in Pharmacies, Technical Assistance Bulletin on Quality Assurance for Pharmacy-Prepared Sterile Products, Technical Assistance Bulletin on Handling Cytotoxic Hazardous Drugs, and Technical Assistance Bulletin on Pharmacy-Prepared Ophthalmic Products.*

35 Compounding Pharmacy Accreditation, Accreditation Commission for Health Care, available at https://www.achc.org/compounding-pharmacy.html (last accessed Apr. 2, 2021).

36 Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients, Senate Hearing 108-378 (Oct. 23, 2003), *available at* https://www.govinfo.gov/content/pkg/CHRG-108shrg90129/html/CHRG-108shrg90129.htm (last accessed Apr. 2, 2021).

37 Compounding and the FDA: Questions and Answers, FDA (Jun. 21, 2018) *available at* https://www.fda.gov/drugs/human-drug-compounding/compounding-and-fda-questions-and-answers (last accessed Apr. 2, 2021).

38 Jennifer Huizen, What to know about hormonal imbalances, Medical News Today (Jun. 17, 2020), *available at* https://www.medicalnewstoday.com/articles/321486 (last accessed Apr. 2, 2021).

39 A. Ruiz et al. Effectiveness of compounded bioidentical hormone replacement therapy: An observational cohort study, BMC Women's Health. 2011;27(11):1-10.

40 Reed-Kan, D. Natural Hormone Replacement Therapy: What It Is And What Consumers Really Want. Int J Pharmaceutical Compounding. 2001;Sept/Oct:5(5).

41 PDF of NASEM Report (Online Version) pp. 17, 94.

42 Brownstein D. The Miracle of Natural Hormones. West Bloomfield, MI:Medical Alternatives Press;1998.

43 Reiss U. Natural Hormone Balance for Women. New York, NY:Pocket Books;2001.

According to the Report Committee, "millions of men and women have reported using compounded hormone therapy."[44] Patients utilize cBHT therapy for a broad spectrum of health concerns related to hormone imbalances including, *inter alia*, vasomotor symptoms and symptoms of vulvar and vaginal atrophy associated with menopause; symptoms of male hypogonadism and testosterone deficiency; sexual health; joint pain; general chronic pain; insomnia; cardiovascular diseases; and various mental health disorders.[45]

The FDA recognizes that it is impossible for drug manufacturers to meet every conceivable patient need, and that certain patients cannot be treated with an FDA-approved medication.[46] For example, there are no FDA-approved BHT products available on the market for certain diseases, such as gender dysphoria.[47]

Other patients need customized medications. For example, a patient may be allergic to a component in an FDA-approved drug that requires the medication to be made without it, such as lactose, gluten, or a dye.[48] Patients who cannot swallow a tablet or capsule (*e.g.*, elderly patients, children) may need a medicine to be compounded in a liquid dosage form.[49] A patient may need an exact strength or dosage that is not commercially available.[50] A patient may need a drug that is currently in shortage or that has been discontinued by the manufacturer.[51]

The customizable nature of cBHT can address these individual needs. Further, while FDA-approved BHT products are only available in limited dosing formulations and strengths, cBHT medications are available in an array of delivery methods (*e.g.*, capsules, creams, sublinguals, lozenges, and vaginal suppositories) and dose strengths.[52] For example, common compounded formulations include estriol alone, "bi-estrogen" or "bi-est" combinations (estradiol and estriol), or "tri-estrogen" or "tri-est" combinations (estrone, estradiol, and estriol), as well as progesterone, testosterone, and dehydroepiandrosterone ("DHEA").[53] The ability to treat patients with a customized dose and/or formulation is in some cases the only way to successfully keep patients on therapy.[54]

Without cBHT, these patients would be unable to receive the medications their physician determined they need to address their health conditions and improve their quality of life. Of note, an analysis of women's motivations for using cBHT found that women decide to use cBHT due to the "persistence of menopausal symptoms, the side effects of conventional [hormone treatments], and a personal preference for CBHT."[55] These benefits and treatment options would not be available if unable to receive cBHT.

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44 PDF of NASEM Report (Online Version) p. 1.

45 PDF of NASEM Report (Online Version) p. 6.

46 Compounding and the FDA: Questions and Answers, FDA (Jun. 21, 2018) *available at* https://www.fda.gov/drugs/human-drug-compounding/compounding-and-fda-questions-and-answers (last accessed Apr. 2, 2021).

47 PDF of NASEM Report (Online Version) p. 7.

48 Compounding and the FDA: Questions and Answers, FDA (Jun. 21, 2018) *available at* https://www.fda.gov/drugs/human-drug-compounding/compounding-and-fda-questions-and-answers (last accessed Apr. 2, 2021); Frequently Asked Questions About Pharmaceutical Compounding, American Pharmacists Association, *available at* https://www.pharmacist.com/frequently-asked-questions-about-pharmaceutical-compounding (last accessed Apr. 2, 2021).

49 Compounding and the FDA: Questions and Answers, FDA (Jun. 21, 2018) *available at* https://www.fda.gov/drugs/human-drug-compounding/compounding-and-fda-questions-and-answers (last accessed Apr. 2, 2021).

50 Frequently Asked Questions About Pharmaceutical Compounding, American Pharmacists Association, *available at* https://www.pharmacist.com/frequently-asked-questions-about-pharmaceutical-compounding (last accessed Apr. 2, 2021).

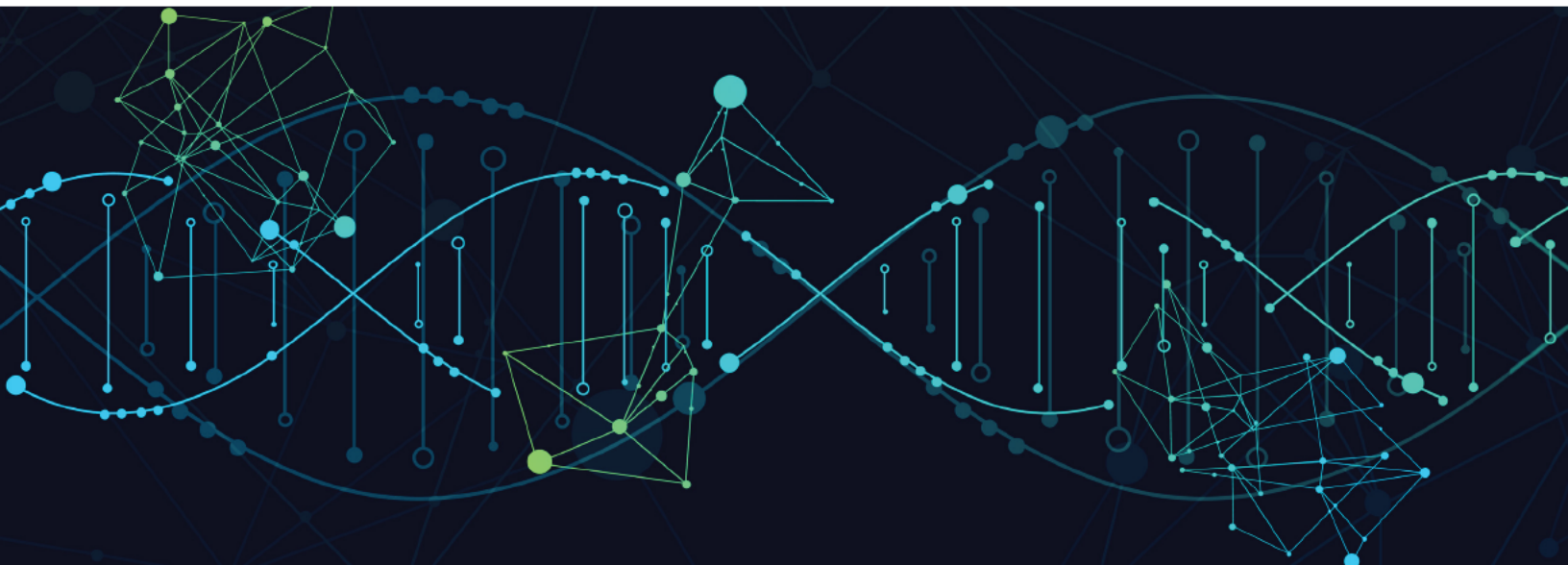
51 Frequently Asked Questions About Pharmaceutical Compounding, American Pharmacists Association, *available at* https://www.pharmacist.com/frequently-asked-questions-about-pharmaceutical-compounding (last accessed Apr. 2, 2021).

52 PDF of NASEM Report (Online Version) pp. 96-100; Ruiz A, et al. Effectiveness of Compounded Bioidentical Hormone Replacement Therapy: An Observational Cohort Study. *BMC Women's Health.* 2011;11:27.

53 Thompson JJ, Ritenbaugh C, Nichter M. Why women choose compounded bioidentical hormone therapy: lessons from a qualitative study of menopausal decision-making. BMC Womens Health. 2017;97(17).

54 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), Exhibit 1-K: Statement of Dr. Peet ("Only approximately half of the patients treated with commercially available progestins can tolerate the hormone because the side effects are so severe that they cause patients to discontinue treatment."). Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), Exhibit 1-A: Statement of Dr. Baker ("Compounded progesterone in topical creams or oral troches are able to bypass many of these side effects.").

55 Thompson JJ, Ritenbaugh C, Nichter M. Why women choose compounded bioidentical hormone therapy: lessons from a qualitative study of menopausal decision-making. BMC Womens Health. 2017;97(17).



The Process of Prescribing and Dispensing cBHT Today

The process of prescribing and dispensing cBHT to patients is consistent with the traditional and well-accepted relationship among the physician, pharmacist, and patient. That is, the duty of the physician is to determine what therapy is in the best interest of the patient's health. If it is determined that hormones are the best course of therapy, the physician then decides if premanufactured or compounded hormones are necessary to best fit the patient's need.[56] For a significant number of patients, premanufactured bioidentical hormones are prescribed.[57] The duty of the pharmacist is to facilitate the prescriber's order after verifying that it is suitable for the individual patient, and to advise the patient on the proper use of thier medication.[58] Finally, the duty of the patient is to pay careful attention to their symptoms and to maintain open communication about their therapy with their physician and pharmacist.[59]

First, the prescriber evaluates the symptoms of the patient and conducts an examination, including laboratory testing in some cases, to determine if the patient is suffering from a condition appropriately treated by hormone supplementation.[60] If the physician determines that hormone therapy is appropriate, he or she may prescribe commercially-available bioidentical products (*e.g.*, oral micronized progesterone) or cBHT.[61] If cBHT is determined to be the treatment of choice, the physician will contact the pharmacy and provide the necessary prescription information, either directly or in the form of a prescription, to a compounding pharmacist. The compounding pharmacist verifies whether the order is appropriate with the physician, given the information provided as to the specific hormone requested, strength, dosage form, directions for use, and quantity. Augmented by computer software, the pharmacist also evaluates the patient's file for drug interactions, duplicate therapy, interactions with preexisting conditions, clinical abuse or misuse, duration of therapy, and medical allergies.[62] Once the pharmacist has verified the appropriateness of the order for the patient, the pharmacist compounds the medication. Before providing the medication to the patient, the pharmacist advises him or her on its appropriate use.[63]

The process does not end once the pharmacist dispenses the medication, however. Patients on cBHT are monitored by their prescribers to ensure that the medication is working in a manner that minimizes toxicity and maximizes clinical benefit.[64] The patient's laboratory values are periodically checked against baseline and previous levels to identify potential toxicities and ensure adequate levels for clinical endpoints, dependent on the therapy and patient needs.[65] Doses are occasionally adjusted to ensure that the dosage strength is kept the minimum required to meet the patient's needs. Patients should communicate openly with their doctors and pharmacists about their symptoms and any negative side effects they are experiencing throughout treatment.[66]

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56 Patient-Physician Relationships: Code of Medical Ethics Opinion 1.1.1., American Medical Association, *available at* www.ama-assn.org/delivering-care/ethics/patient-physician-relationships (last accessed Apr. 2, 2021).

57 The Top 200 of 2021, ClinCalc, *available at* https://clincalc.com/DrugStats/Top200Drugs.aspx (last accessed Apr. 2, 2021).

58 Ruiz A., et al. Effectiveness of compounded bioidentical hormone replacement therapy: An observational cohort study. BMC Women's Health. 2011;27(11):1-10.

59 Ruiz A., et al. Effectiveness of compounded bioidentical hormone replacement therapy: An observational cohort study. BMC Women's Health. 2011;27(11):1-10.

60 Hertoghe T. The Hormone Solution: Stay Younger Longer with Natural Hormone and Nutrition Therapies. New York, NY: Harmony Books;2002; Reiss U. Natural Hormone Balance for Women. New York, NY: Pocket Books;2001; Brownstein D. The Miracle of Natural Hormones. West Bloomfield, MI: Medical Alternatives Press;1998; Schwartz E. The Hormone Solution: Naturally Alleviate Symptoms of Hormone Imbalance from Adolescence Through Menopause. New York, NY: Warner Books;2002.

61 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), Exhibit 1-F: Statement from Christine Farrell, p.100.

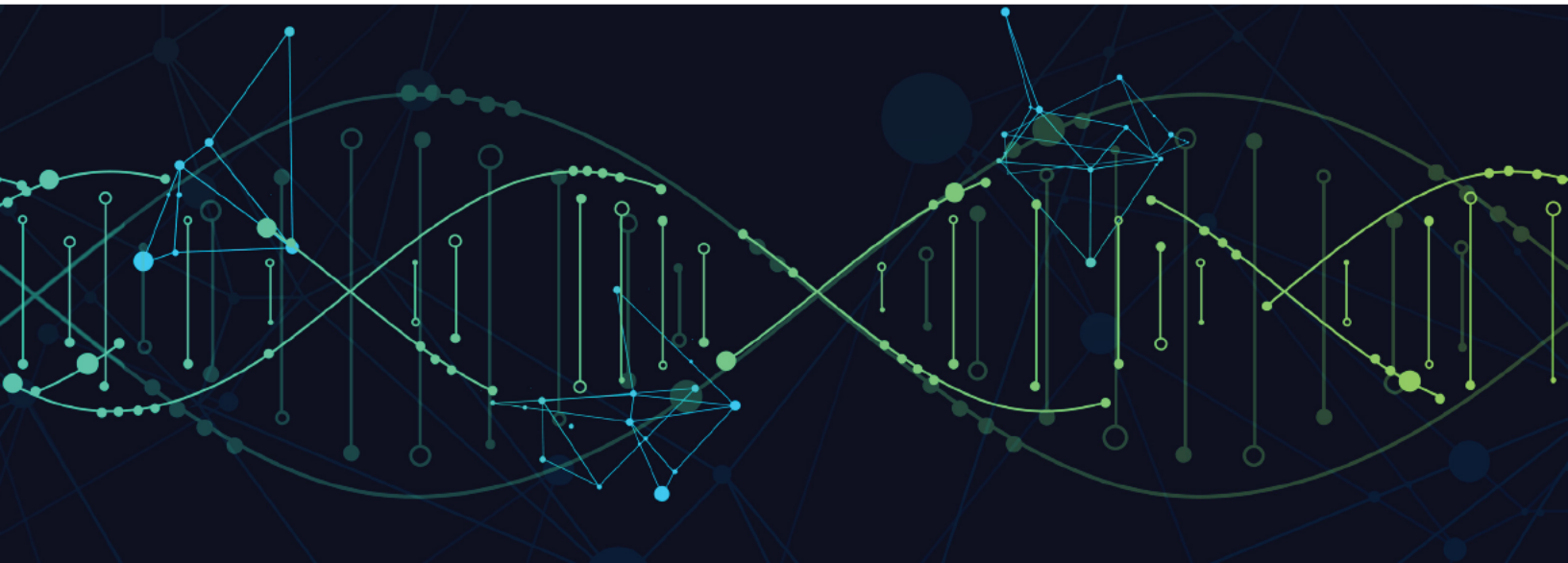
62 The Pharmacy Compounding Professional's Code of Ethics: Responsibilities to One's Patents, Self, Colleagues, and Profession, *available at* https://a4pc.org/Common/Uploaded%20files/2021_APC-Code-of-Ethics.pdf (last accessed Apr. 2, 2021); Haumschild MJ, et al. Pharmacy-based Computer System for Monitoring and Reporting Drug Interactions. Am J Hosp Pharm. 1987;44(2):345-8.

63 Ruiz A., et al. Effectiveness of compounded bioidentical hormone replacement therapy: An observational cohort study. BMC Women's Health. 2011;27(11):1-10.

64 Ruiz A., et al. Effectiveness of compounded bioidentical hormone replacement therapy: An observational cohort study. BMC Women's Health. 2011;27(11):1-10.

65 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), Exhibit 1-G: Statement from Laura Grant, p. 106.

66 Hertoghe T. The Hormone Solution: Stay Younger Longer with Natural Hormone and Nutrition Therapies. New York, NY: Harmony Books;2002; Reiss U. Natural Hormone Balance for Women. New York, NY: Pocket Books;2001; Brownstein D. The Miracle of Natural Hormones. West Bloomfield, MI: Medical Alternatives Press;1998; Schwartz E. The Hormone Solution: Naturally Alleviate Symptoms of Hormone Imbalance from Adolescence Through Menopause. New York, NY: Warner Books;2002.



The NASEM Report

In September 2018, the FDA contracted with NASEM to appoint an ad hoc Committee to review the uses of cBHT preparations and "assess the clinical utility" of treating patients with cBHT products.[67]

As an initial matter, there is no standard definition of "clinical utility" in the medical field. Recognizing that "no standardized definition exists" for the term, the 12-person Committee decided that it would develop its own definition for the purposes of the Report.[68] Mirroring the language of FDA requirements for new drug approval, as discussed in greater detail below, the Committee ultimately defined "clinical utility" as "a multidimensional construct that reflects evidence about safety, effectiveness, and therapeutic need."[69]

The Committee held nine closed-session meetings, as well as five public information-gathering sessions wherein key stakeholders—including Jane Axelrad, a former FDA official[70] and outspoken critic of compounding, as discussed in greater detail below—were invited to present their research and thoughts on the topic.[71] It solicited peer-reviewed literature, research reports, books, and other quantitative data from key stakeholders including, *inter alia*, the Professional Compounding Centers of America, the National Association of Boards of Pharmacy, compounding advocacy organizations, nonprofit wellness organizations, women's health advocacy groups, and medical prescribers and researchers of cBHT.[72] The Committee also reviewed testimonies submitted by "thousands" of patients who use cBHT.[73] The Committee received a number of suggested articles and other references from study stakeholders, in addition to the hundreds of articles that it identified through its own literature review process.[74]

Out of that vast body of literature submitted to the Committee, the Committee identified a total of 13 studies that it deemed to be "of adequate methodologic rigor for inclusion in its review of safety and effectiveness of these preparations."[75]

Relying upon those 13 studies—which only addressed five variations of cBHT[76] as support—the Committee concluded that a "dearth of evidence" exists to "support many of the marketed claims for the clinical utility of cBHT as a treatment of menopausal and male hypogonadism symptoms."[77] Ultimately, the Committee offered six recommendations that aimed to broadly restrict the use of cBHT and encourage "assessments of its difficulty to compound, and additional education, oversight, and research."[78] Those recommendations are as follows:[79]

1. **Restrict the use of cBHT preparations** to "documented allergy to an active pharmaceutical ingredient or excipient of [FDA]-approved drug product, or a documented requirement for a different dosage form."
2. **Review select bioidentical hormone therapies and dosage forms as candidates for the FDA "Difficult to Compound" List,** including estradiol, estrone, estradiol cypionate, estriol, dehydroepiandrosterone, pregnenolone, progesterone, testosterone, testosterone cypionate, and testosterone propionate.
3. **Improve education for prescribers and pharmacists who market, prescribe, compound, and dispense cBHT preparations** by, *inter alia*, implementing state-level certifications for cBHT prescribers; encouraging nonprofit professional societies to expand evidence-based guidelines and best practices for cBHT prescribers; and requiring pharmacists to complete "more in-depth" training on compounding hormone preparations.
4. **Additional federal and state-level oversight should be implemented to better address public health and clinical concerns regarding the safety and effectiveness of cBHT** including, *inter alia*: mandating that all cBHT preparations dispensed from 503A pharmacies or supplied from 503B outsourcing facilities must include standardized inserts and boxed warnings; requiring all states to immediately adopt USP <795> and <797> standards to ensure the quality of dispensed sterile and nonsterile cBHT preparations; and modifying the standard MedWatch form to adequately collect and track adverse events data related to cBHT use. More specifically, the Committee stated that this increased oversight should include the following requirements:

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67 PDF of NASEM Report (Online Version) p. 18.
68 PDF of NASEM Report (Online Version) p. 20.
69 PDF of NASEM Report (Online Version) p. 4; *see* Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 14.
70 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 17 n.18.
71 PDF of NASEM Report (Online Version) pp. 21-22.
72 PDF of NASEM Report (Online Version) pp. 22-23.
73 PDF of NASEM Report (Online Version) p. 23.
74 PDF of NASEM Report (Online Version) p. 139.
75 PDF of NASEM Report (Online Version) p. 140.
76 PDF of NASEM Report (Online Version) p. 95.
77 PDF of NASEM Report (Online Version) pp. 10-15.
78 PDF of NASEM Report (Online Version) p. 10.
79 PDF of NASEM Report (Online Version) pp. 10-15.

a. Standardized insert for all dispensed cBHT preparations from all 503A pharmacies and 503B outsourcing facilities. The Committee recommended that the standardized insert should include, *inter alia*, (i) 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; (ii) indications and guidance for use (administration), dosage strength and form, statement of compliance to CGMP or USP standards, beyond-use date, contraindications, side effects, caution for potential adverse effects, and instructions on how to report adverse events; and (iii) boxed warnings for potential adverse effects for compounded prescriptions that include estrogens (estradiol, estriol, estrone) and androgens (testosterone).

b. Increased adverse event reporting requirements. The Committee recommended that all compounders should be required to monitor and report all adverse events of cBHT preparations to state boards of pharmacy, MedWatch, and the FDA Adverse Event Reporting System ("FAERS"). The Committee further recommended that compounders should submit annual adverse event reports for non-severe and non-life-threatening events, and that all such reports should include information on the frequency, type, and severity of adverse events related to the use of cBHT.

3. **Collect and disclose conflicts of interest** arising from financial relationships between cBHT prescribers/compounders and cBHT companies, make them publicly available, and disclose them to the patients at the point of care.

4. **Strengthen and expand the evidence base on the safety, effectiveness, and use of cBHT preparations** by encouraging public agencies (*e.g.*, the National Institutes of Health) to increase funding for research to address gaps in the evidence base.

On July 1, 2020, the Committee published its recommendations.[80] We discuss the shortcomings of the Report development process and identify the flaws in the Committee's conclusions throughout the remainder of this white paper.

Bias May Have Influenced the Conclusions and Recommendations of the Committee

With regard to evidence-based medicine, it has been recognized that:[81]

> "In research, bias occurs when 'systematic error [is] introduced into sampling or testing by selecting one outcome or answer over others.' Bias can occur at any phase of research, including study design or data collection, as well as in the process of data analysis and publication…As some degree of bias is nearly always present in a published study, readers must also consider how bias might influence a study's conclusions."

And with regard to the Report specifically, NASEM had an obligation to ensure that the Report was unbiased and objective. NASEM is subject to the provisions of the Federal Advisory Committee Act ("FACA"), which require that NASEM must **"provide independent, unbiased advice without actual or perceived interference or management of the outcome (findings and recommendations)."**[82] Further, in its acquisition plan selecting NASEM to conduct the Study, FDA stated that:[83]

> "Due to the nature of the requirement, **it is in the public interest to receive the independent advice of unparalleled objectivity of the highest quality that provides an inherent degree of acceptability.**"

Given the implications of the NASEM Report recommendations on the availability of cBHT and the practice of medicine, if implemented, it is critical that any potential bias be examined to determine how it influenced the Committee's conclusions. However, as discussed below, multiple instances of the FDA influencing the composition of the Committee and its review team—in addition to the final recommendations of the Report itself—have come to light. The Committee and its review team includes individuals who may be implicitly (or explicitly) biased against the use of cBHT by virtue of their participation in organizations that oppose compounding or their involvement with large pharmaceutical companies and the FDA itself. Moreover, that the Committee has little, if any, practical or clinical experience with cBHT may manifest as an aversion to compounding in light of popular misconceptions about the practice, described in greater detail below.

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80 Report Release Webinar: Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy," NASEM (July 1, 2020), *available at* https://www.nationalacademies.org/event/07-01-2020/report-release-webinar-clinical-utility-of-treating-patients-with-compounded-bioidentical-hormone-replacement-therapy (last accessed Apr. 2, 2021).

81 Pannucci CJ, Wilkins EG. Identifying and avoiding bias in research. Plast Reconstr Surg. 2021;126(2):619-625.

82 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 250 (emphasis added).

83 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 227 (emphasis added).

The Committee and its Review Team Included Individuals Who May Have Been Biased Against cBHT

For at least the past two decades, both the FDA and pharmaceutical manufacturers have worked to discredit compounding and to reduce access to cBHT.

For example, since the 1940s, Wyeth Pharmaceuticals has sold Premarin, the world's first conjugated synthetic estrogen medication and one of the drugs studied in the infamous Women's Health Initiative ("WHI") study, described in more detail below.[84] Premarin was Wyeth's first "blockbuster" drug (*i.e.*, drug to reach $1 billion in sales), and it was the #1 prescribed drug in the U.S. for a number of years.[85] However, after the WHI study linked Premarin to increased risk of breast cancer and cardiac disease in 2002 (also described in more detail below), Wyeth's sales began to plummet.[86] Wyeth's global sales dropped from over $2 billion in 2001 to $880 million in 2004.[87] ***One year after that decrease in sales***, in 2005, Wyeth submitted a citizen petition to the FDA demanding that it "[i]nitiate enforcement actions in the form of seizures, injunctions and/or warning letters" against cBHT pharmacies that Wyeth claimed "are simply trying to dupe an unsuspecting patient population."[88] Notably, Wyeth ***proffered the same (but incorrect) position held by the Committee that compounded BHT must be held to the same standards as FDA-approved drugs*** in terms of safety and efficacy data—only after its own hormone product, Premarin, failed.[89]

In 2007, Congress held a hearing entitled, "Bio-Identical Hormones: Sound Science or Bad Medicine?," in which Steve Galson, then-Director of CDER at FDA, expressed the FDA's view that compounded drugs are "new drugs" that are subject to the new drug, adulteration, or misbranding provisions of the FD&C Act despite contemporaneous judicial rulings to the contrary.[90] And with regard to the Wyeth Citizen Petition, Mr. Galson asserted that although the "majority" of the 68,000 comments received by the FDA asked that the petition be denied, it was "noteworthy" that the FDA received "some" comments from prescribers and pharmacists that were concerned about the use of cBHT products.[91] Although the FDA ultimately rejected Wyeth's Citizen Petition on technical grounds, it continues to share Wyeth's position today.[92] It is the FDA's current view that since "compounded BHRT products are not approved by the agency, there is no assurance of safety and efficacy."[93] Further, the FDA asserts that compounded drugs, in general, can "unnecessarily expose[] patients to potentially serious health risks."[94]

In light of the foregoing, it is notable that most Committee members have close ties to large pharmaceutical companies (for which the cessation of compounding practices may be favorable), have served in organizations that have released position statements against cBHT, or are former employees of the FDA, whose position on cBHT is well-understood. As shown below, the Committee members have several organizational ties that could have served as a source for potential bias against cBHT.

- Dr. Lesley H. Curtis serves as the Interim Director of the Duke Clinical Research Institute at Duke University. Her "biosketch" states that 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."[95]
- Dr. Susan S. Ellenberg is a Professor of Biostatistics, Medical Ethics, and Health Policy at the University of Pennsylvania Perelman School of Medicine. Prior to joining Penn, she held leadership positions at the FDA. Dr. Ellenberg "works closely with several pharmaceutical companies, including Merck, Bristol-Myers Squibb, and Marinus Pharmaceuticals."[96]
- Dr. Adel Karara is a Professor of Pharmaceutical Sciences at University of Maryland, and a member of the FDA Pharmaceutical Science and Clinical Pharmacology Advisory Committee for oncology drugs. Prior to becoming a professor, Dr. Karara held senior positions at various pharmaceutical companies, including Roche, Berlex, and Novartis.[97] Dr. Karara has also served on the Clinical Pharmacology Technical Group segment of the Pharmaceutical Research and Manufacturers of America ("PhRMA"), a professional trade organization that "represents the country's leading innovative biopharmaceutical research companies."[98]

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84 Stephen K. Ritter, Premarin—Purpose Hormone, Chemical & Engineering News (Jun. 20, 2005), *available at* https://cen.acs.org/articles/83/i25/Premarin.html (last accessed Apr. 2, 2021).

85 Deena Beasely, Wyeth's Pristiq helps menopause hot flashes-trials, Reuters (May 9, 2007), *available at* https://www.reuters.com/article/idUSN0136556020070508 (last accessed Apr. 2, 2021). Stephen K. Ritter, Premarin—Purpose Hormone, Chemical & Engineering News (Jun. 20, 2005), *available at* https://cen.acs.org/articles/83/i25/Premarin.html (last accessed Apr. 2, 2021).

86 Melody Petersen, Wyeth Stock Falls 24% After Report, New York Times (July 10, 2002), *available at* https://www.nytimes.com/2002/07/10/us/wyeth-stock-falls-24-after-report.html (last accessed Apr. 2, 2021).

87 Stephen K. Ritter, Premarin—Purpose Hormone, Chemical & Engineering News (June 20, 2005), *available at* https://cen.acs.org/articles/83/i25/Premarin.html (last accessed Apr. 2, 2021)..

88 D Dave Tuttle, Health Freedom Under Attack! Drugmaker Seeks to Deny Access to Bioidentical Hormones, Le Magazine (Aug. 2006), *available at* https://www.hdrx.com/documents/Wyeth%20Attacks%20BHRT.pdf (last accessed Apr. 2, 2021).

89 Dave Tuttle, Health Freedom Under Attack! Drugmaker Seeks to Deny Access to Bioidentical Hormones, Le Magazine (Aug. 2006), *available at* https://www.hdrx.com/documents/Wyeth%20Attacks%20BHRT.pdf (last accessed Apr. 2, 2021).

90 *See* Bio-Identical Hormones: Sound Science or Bad Medicine?, Senate Hearing 110-129 (Apr. 19, 2017), *available at* https://www.govinfo.gov/content/pkg/CHRG-110shrg37150/html/CHRG-110shrg37150.htm (last accessed Apr. 2, 2021).

91 *See* Bio-Identical Hormones: Sound Science or Bad Medicine?, Senate Hearing 110-129 (Apr. 19, 2017), *available at* https://www.govinfo.gov/content/pkg/CHRG-110shrg37150/html/CHRG-110shrg37150.htm (last accessed Apr. 2, 2021).

92 Wyeth Loses Citizen Petition Battle But Wins War Over Compounded Hormones, In Vivo (Jan. 14, 2008), *available at* https://invivo.pharmaintelligence.informa.com/PS049195/Wyeth-Loses-Citizen-Petition-Battle-But-Wins-War-Over-Compounded-Hormones (last accessed Apr. 2, 2021). In its response letter, FDA noted that it denied Wyeth's petition because "[r]equests for the Agency to initiate enforcement actions are not within the scope of FDA's citizen petition procedures. *See* 21 CFR 10.30(k)." FDA Letter to Wyeth re: Citizen Petition (Jan. 9, 2008).

93 Janet Woodcock M.D., Statement on improving adverse event reporting of compounded drugs to protect patients, FDA (Sept. 9, 2019), *available at* https://www.fda.gov/news-events/press-announcements/statement-improving-adverse-event-reporting-compounded-drugs-protect-patients (last accessed Apr. 2, 2021).

94 Compounding and the FDA: Questions and Answers, FDA (June 21, 2018), *available at* https://www.fda.gov/drugs/human-drug-compounding/compounding-and-fda-questions-and-answers (last accessed Apr. 2, 2021).

95 PDF of NASEM Report (Online Version) p. 254.

96 PDF of NASEM Report (Online Version) p. 255.

97 PDF of NASEM Report (Online Version) p. 256.

98 About, PhRMA, *available at* https://www.phrma.org/en/About (last accessed Apr. 2, 2021).

- Dr. Aaron S. Kesselheim is a Professor of Medicine at the Harvard Medical School and a faculty member in the Division of Pharmacoepidemiology and Pharmacoeconomics in the Department of Medicine at Brigham and Women's Hospital. He is also a member of the FDA Peripheral and Central Nervous System Advisory Committee.[99]
- Dr. Robert B. MacArthur is the Pharmacy Director at the Rockefeller University Hospital. He previously held positions at Sandoz and Novartis, in addition to various small- and mid-sized pharmaceutical companies, such as Systems Medicines, CTI, and Aeson Therapeutics.[100]
- Dr. Jose Manautou is a Professor of Toxicology and Interim Head of the Department of Pharmaceutical Sciences at the University of Connecticut, and a member of the FDA Nonprescription Drugs Advisory Committee.[101]
- Dr. Nancy King Reame is the Mary Lindsay Professor Emerita of Health Promotion and Risk Reduction in the School of Nursing at Columbia University.[102] She served as a member of the Board of Trustees for the North American Menopause Society ("NAMS"), which in 2017 released a position statement on compounded hormone therapy asserting that "prescribers should only consider compounded [hormone therapy] if women cannot tolerate a government-approved therapy for reasons such as allergies to ingredients or for a dose or formulation not currently available in government-approved therapies."[103]
- Dr. David R. Rubinow is the Meymandi Professor and Chair of the Department of Psychiatry at the University of North Carolina at Chapel Hill's School of Medicine. His "biosketch" states that he 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)."[104]

Further, the FDA made several recommendations as to who should serve on NASEM's Committee or opine as subject matter "experts."[105] The FDA recommended that NASEM include Jane Axelrad, James H. Liu, Nanette Santoro, and Adel H. Karara.[106] All of these individuals participated in some aspect of the development of the Report—Dr. Karara was actually named as a member of the Committee; Jane Axelrad and James H. Liu were selected as reviewers, as discussed in more detail below; and Nanette Santoro wrote one of the 13 articles that the Committee relied upon in drawing its conclusions and providing recommendations on cBHT.

In light of the foregoing, it is imperative that readers of the NASEM Report consider how the biases of both the Committee and those who participated in other capacities may have influenced the recommendations in the Report. This consideration of potential bias is especially important given that most, if not all, of the Committee members appear to lack any real-world experience prescribing or dispensing cBHT to patients, as discussed below.

The Committee Did Not Include Any Prescribers or Pharmacists with Substantive, Patient-Facing Experience with cBHT

It appears the Committee was comprised of individuals who had little, if any, practical or substantive experience with the topic on which they were opining: cBHT.

With the exception of two individuals—Dr. Donald R. Mattison, the Chief Medical Officer and Senior Vice President at Risk Sciences International, and Dr. Robert B. MacArthur, the Pharmacy Director at the Rockefeller University Hospital—every member of the Committee is in academia.[107] Upon review of the Committee members' "biosketches" included in the Report, only one Committee member is currently treating patients.[108] No one else on the Committee is an active prescriber or a pharmacist with patient-facing experience, let alone experience preparing BHT compounds.[109] In fact, one Committee member lacks any medical training whatsoever.[110]

While each member of the Committee may be experts in their own fields, none of them have studied the safety and efficacy of cBHT firsthand or engaged in the practice of prescribing or dispensing cBHT as a practicing medical professional. In essence, the Committee was asked by the FDA to develop recommendations on a topic about which it knew little. Additionally, as described above, the Committee members were affiliated with organizations that could have contributed significant bias, as their education and perspectives accumulated therein may be reflective of the same opinions of those institutions (*e.g.*, FDA, NAMS).

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99 PDF of NASEM Report (Online Version) pp. 256-257.
100 PDF of NASEM Report (Online Version) p. 257.
101 PDF of NASEM Report (Online Version) p. 258.
102 PDF of NASEM Report (Online Version) p. 258.
103 The NAMS 2017 Hormone Therapy Position Statement Advisory Panel, The 2017 hormone therapy position statement of The North American Menopause Society, MENOPAUSE (Jul. 2017), pp. 728-753.
104 PDF of NASEM Report (Online Version) p. 259.
105 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 7.
106 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 5.
107 PDF of NASEM Report (Online Version) Appendix D.
108 *See* PDF of NASEM Report (Online Version), Appendix D: Aaron S. Kesselheim, M.D., J.D., M.P.H.
109 *See* PDF of NASEM Report (Online Version), Appendix D.
110 *See* PDF of NASEM Report (Online Version), Appendix D: Jennifer Fishman, Ph.D.

Jane Axelrad, Former FDA Official and Outspoken Critic of cBHT, Played Multiple Key Roles in the Development of the NASEM Report

Based upon a review of the documents obtained by Reed Smith via its FOIA request,[111] it is evident that the FDA sought to guarantee that the Committee reached the conclusion that the FDA wanted by ensuring that its proxy—Jane Axelrad, the recently-retired former FDA lead on pharmaceutical compounding—was deeply involved in the development of the Report.

From 1995 to 2012, Jane Axelrad worked as the Associate Director for Policy for Drug Evaluation and Research ("CDER") at FDA.[112] From 2012 to 2016, Ms. Axelrad was the FDA "lead for the pharmacy compounding initiative where she led the development of numerous regulations and guidance documents to implement the drug compounding provisions of the DQSA" and "oversaw the [FDA's] compounding inspection and enforcement efforts."[113] Since retiring from her position as the "FDA lead on pharmacy compounding" in April 2016, Ms. Axelrad has publicly criticized the compounding industry. For example, in a 2017 opinion piece for The Hill, Ms. Axelrad asserted—without providing supporting evidence—that "many" compounding pharmacies operate in violation of federal compounding laws and that absent FDA oversight, compounders would not be incentivized to adhere to quality and safety standards:[114]

> "Compounded drugs are not FDA-approved. They are supposed to be customized to meet an individual patient's needs when an approved product cannot, but **many pharmacies are engaging in mass-production of drugs without obtaining individual prescriptions.**"
>
> "The **compounding pharmacy industry is trying to convince Congress** to prohibit the FDA from enforcing the prescription requirement that Congress instituted 20 years ago and re-affirmed just four years ago."
>
> **"If Congress eliminates the prescription requirement, it would remove any incentive for compounders to register as outsourcing facilities and comply with the standards that are necessary for the safety of higher volume, non-individualized compounding."**

Thus, Ms. Axelrad's bias against compounding was well-known long before the NASEM Report was commissioned. Indeed, one contemporaneous respondent to her 2017 opinion piece commented that Ms. Axelrad sounded "an awful [lot] like a lobbyist for drug companies."[115]

Despite Ms. Axelrad's public opposition to compounding and her extensive career with the FDA—or perhaps ***because*** of those reasons—the FDA specifically sought to ensure that she was involved in the development of the NASEM Report. On November 9, 2018, Gabrielle Cosel with the FDA explained to Ms. Axelrod that NASEM asked for recommendations for experts to serve on two upcoming committees (the cBHT study at issue and another on compounded topical pain medications), and that FDA wanted to proffer her as an expert in the cBHT study.[116] Ms. Axelrod responded:[117]

> "I don't think I can do it as **I have a client interested in bioidentical hormones.** I nominated 5 people for that, 4 outside doc experts and one I would think that would be a conflict. Maybe I could do pain creams? You will have to decide as I'm about to board a plane to come home from CA. Talk soon."

Thus, in its November 9, 2018 "recommendations for NASEM Committees," the FDA proffered Ms. Axelrad as a recommended expert on a committee related to compounded topical pain creams because "she has indicated she may have a current business conflict with regard to hormone therapy."[118]

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111 On March 4, 2021, Reed Smith LLP submitted a supplement to its August 17, 2020 Comment to the FDA regarding the NASEM Report. In July 2020, to gather more information on the development of the Report, Reed Smith submitted a substantial Freedom of Information ("FOIA") request to the FDA requesting communications between the FDA, NASEM, and other relevant individuals and organizations. Its findings from the produced materials were set forth in an extensive report that presented various sources of bias that could have affected NASEM's Report and the Committee's final recommendations.

112 Jane Axelrad, J.D., Association for Accessible Medicines, *available at* https://www.grxbiosims.org/speakers/jane-axelrad-j-d/ (last accessed Apr. 2, 2021).

113 Jane Axelrad, J.D., Association for Accessible Medicines, *available at* https://www.grxbiosims.org/speakers/jane-axelrad-j-d/ (last accessed Apr. 2, 2021).

114 Jane Axelrad, Congress, prevent another outbreak – Don't roll back drug contamination protections, The Hill (Jul. 10, 2017), *available at* https://thehill.com/blogs/pundits-blog/healthcare/341145-why-congress-cant-rollback-protections-from-dangerous-drugs?rl=1 (last accessed Apr. 2, 2021) (emphasis added).

115 Jane Axelrad, Congress, prevent another outbreak – Don't roll back drug contamination protections, The Hill (Jul. 10, 2017), *available at* https://thehill.com/blogs/pundits-blog/healthcare/341145-why-congress-cant-rollback-protections-from-dangerous-drugs?rl=1 (emphasis added) (last accessed Apr. 2, 2021).

116 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 268.

117 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 268 (emphasis added).

118 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 265.

Although she declined to participate as a Committee member, Ms. Axelrad nevertheless contributed to the NASEM Report in multiple ways. At the Committee's June 27, 2019 open session, Ms. Axelrad delivered a presentation to the Committee entitled, "Understanding the List of Difficult to Compound Drug Products."[119] In 2014, when Ms. Axelrad was serving as the FDA lead on compounding, several hormones were nominated for the Difficult to Compound list—including 9 of the 11 hormones that NASEM ultimately included in its recommendation that the FDA's Pharmacy Compounding Advisory Committee ("PCAC") should review for the FDA "Difficult to Compound" List.[120] In her presentation, Ms. Axelrad advocated for the Committee to find those same hormones that were nominated in 2014 too difficult to compound, including bioidentical hormone pellets, estradiol, progesterone, testosterone, and estriol.[121]

As an initial matter, it is unclear how Ms. Axelrad's presentation on the Difficult to Compound list is relevant to the Study, given the Committee's directives set forth below:[122]

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 the patients; and
  - The patient populations that might need a compounded BHRT drug product in lieu of a U.S. Food and Drug Administration-approved drug product

As shown in Box 1-1, the Committee's statement of task did not include requests for information about the FDA's Difficult to Compound list or any other regulatory question. Indeed, it appears that there was some concern about the relevance of Ms. Axelrad's presentation at some point, as Ms. Axelrad found it necessary to include a slide in her presentation to the Committee entitled, "How does this relate to the work of the Committee?"[123]

The rationale behind the Committee's decision to include Ms. Axelrad as a speaker becomes clear when one considers that her out-of-scope presentation to the Committee is consistent with the position she held during her tenure as the FDA's lead on compounding. For example, on February 27, 2014, Ms. Axelrod gave a presentation on Sections 503A and B of FD&C Act to the FDA Joint Commission in her capacity as CDER's Associate Director for Policy.[124] In her presentation, Ms. Axelrad publicly asserted—without providing support for her claims—that:[125]

> "The new law leaves some issues unresolved…**Compounders may seek to hide out in the traditional compounding category and escape detection**…What does this mean for you? **FDA-approved drugs should be used wherever possible.**"

119 *See* Jane A. Axelrad, Understanding the List of Difficult to Compound Drug Products, Axelrad Solutions LLC (June 27, 2019), *available at* https://www.nationalacademies.org/event/06-27-2019/docs/DB151F97635AA45446B74F858FB5ABB9C6B4E2D21F88 (last accessed Apr. 2, 2021).

120 *See* Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act; Request for Nominations, FDA (Dec. 4, 2013), *available at* https://www.regulations.gov/document/FDA-2013-N-1523-0001/comment (last accessed Apr. 2, 2021). Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 17.

121 Jane A. Axelrad, Understanding the List of Difficult to Compound Drug Products, Axelrad Solutions LLC (June 27, 2019), *available at* https://www.nationalacademies.org/event/06-27-2019/docs/DB151F97635AA45446B74F858FB5ABB9C6B4E2D21F88 (last accessed Apr. 2, 2021) p. 9.

122 PDF of NASEM Report (Online Version) p. 19.

123 Jane A. Axelrad, Understanding the List of Difficult to Compound Drug Products, Axelrad Solutions LLC (June 27, 2019), *available at* https://www.nationalacademies.org/event/06-27-2019/docs/DB151F97635AA45446B74F858FB5ABB9C6B4E2D21F88 (last accessed Apr. 2, 2021) p. 19.

124 Jane A. Axelrad, Pharmacy Compounding Legislation and Implementation, FDA (Feb. 27, 2014).

125 Jane A. Axelrad, Pharmacy Compounding Legislation and Implementation, FDA (Feb. 27, 2014) (emphasis added).

And acting on behalf of the FDA at a presentation to PCAC in June 2015, Ms. Axelrad publicly asserted her opinion—again, without providing support for her claims—that even the most highly-skilled compounders lacked the ability to successfully produce those hormones:[126]

> "[W]e have seen drugs and categories of drugs that even drug manufacturers have difficulty getting right. . . .**So I think that there may be certain drugs on the list that we don't think that even a highly skilled compounding operation could do successfully**. . . .[W]e want to eliminate risks to public health that might be associated with compounding difficult-to-compound drugs that we don't think, in most cases, can be compounded safely or provide a safe and effective product."

Ms. Axelrad's position as a presenter in the NASEM Report is indistinguishable from her position as the FDA lead on compounding. As such, Ms. Axelrad's presentation fell far short of the "independent advice of unparalleled objectivity" standard to which the FDA purportedly held NASEM.[127]

Further, Ms. Axelrad's involvement in the Study was not limited to her presentation. Ms. Axelrad was also selected to serve as a reviewer of the draft Report. According to NASEM policy, all reports must "undergo a rigorous, independent external review" by independent experts, and sponsors may not suggest changes in reports.[128] However, as evidenced by the FDA's role in securing Ms. Axelrad's participation in the Report, as well as her public statements both before and after her retirement from the FDA, Ms. Axelrad is a proxy for the FDA—the study sponsor for the Report. Therefore, the Report review process did not meet NASEM's own standards for an independent, objective external review process.

Given Ms. Axelrad's close ties to the FDA and her involvement in the Report as both a presenter and a reviewer, it is not surprising that one of the Committee's final recommendations mirrors the position for which Ms. Axelrad advocated both as the FDA lead on compounding and in her capacity as an "independent expert" for the NASEM Report. Indeed, as noted above, 9 of the 11 hormones that NASEM ultimately recommended for PCAC review had been nominated for the FDA "Difficult to Compound" List ***during Ms. Axelrad's tenure as the FDA lead on compounding***.[129] In sum, by virtue of Ms. Axelrad's involvement alone, it cannot be said that the NASEM Report is free from bias in favor of the FDA, or that the Report was developed "independently."

The Committee's Conclusions Regarding the Safety and Efficacy of cBHT are Flawed

One of the key conclusions underpinning the Committee's recommendations asserts:[130]

> "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."

The Committee is incorrect that evidence is lacking to demonstrate that cBHT is safe and effective. As discussed below, the Committee ignored the body of research and testimony submitted by stakeholders regarding the use of cBHT therapies—evidence of the safety and efficacy of cBHT—and instead relied upon a mere 13 studies to draw that conclusion. In so doing, the Committee ignored that it is not reasonable or practical to apply the standards for FDA-approved drugs to cBHT formulations. As a result, the NASEM Report cannot be said to offer an accurate or complete evaluation of the clinical utility of cBHT.

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126 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 6 n.19 (emphasis added).

127 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 227.

128 Our Study Process, NASEM, *available at* https://www.nationalacademies.org/about/our-study-process (last accessed Apr. 2, 2021).

129 *See* Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act; Request for Nominations, FDA (Dec. 4, 2013), *available at* https://www.regulations.gov/document/FDA-2013-N-1523-0001/comment (last accessed Apr. 2, 2021).

130 PDF of NASEM Report (Online Version) p. 161.

The Definition of "Clinical Utility" Developed and Relied Upon by the Committee Does Not Reflect an Accurate or Complete Representation of the Term

As shown in NASEM Report Box 1-1, recreated above, the Committee was tasked with assessing the "clinical utility" of cBHT. Recognizing that "no standardized definition exists" for the term, the Committee identified over 20 different pieces of literature that "reflect the various components of the term."[131] The Committee set forth an overview of the "main themes of clinical utility" in Box 1-2 of its Report, recreated below:[132]

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

- The current standard of care
- The care setting
- Costs of care and tests
- 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

Instead of relying upon the identified manner in which clinical utility is discussed in the literature, and despite its own admission that the literature supports the use of a broad range of factors, the Committee developed their own definition for "clinical utility." The Committee justified its decision to create its own definition by asserting that existing definitions did not adequately capture all of the components that comprise the term.[133] However, the Committee's stated purpose for ignoring the existing definitions of the term and developing its own definition of "clinical utility" is belied by the Committee's own actions.

Rather than set forth a broad, "all-inclusive" definition that "encompass[es] additional components not necessarily reflected in existing definitions," the Committee narrowly defined "clinical utility" as "a multidimensional construct that reflects evidence about safety, effectiveness, and therapeutic need."[134] And although it recognized the "multidimensional" nature of clinical utility in its invented definition of the term, the Committee ignored this aspect when applying its definition to cBHT. As discussed in greater detail below, one of the Committee's key conclusions underpinning its recommendations is that "**well-designed and properly controlled clinical trials are needed to provide reliable evidence** about the safety and effectiveness of cBHT preparations."[135] The Committee's position appears to be that the clinical utility of cBHT can only be established through controlled clinical trials—contrary to its *own* invented definition of the term as "multidimensional," and its own admission in Box 1-2 that "**the evidence describing the components of clinical utility is <u>not confined</u> to randomized controlled trials.**"[136]

Given that the Committee recognized the need for a broad, "all-inclusive" definition of clinical utility, it is unclear why the Committee ultimately chose to define the term so narrowly—and to apply an even narrower definition in practice—absent involvement by (or bias in favor of) the FDA. Tellingly, the Committee's definition utilizes similar language to that of Section 355 of the FD&C Act, which sets forth the requirements for a new drug to obtain FDA approval (*i.e.*, applicants must show that the new drug is "safe for use" and "effective").[137]

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131 PDF of NASEM Report (Online Version) pp. 19, 217-18.
132 PDF of NASEM Report (Online Version) p. 21 (emphasis added).
133 PDF of NASEM Report (Online Version) p. 218.
134 PDF of NASEM Report (Online Version) p. 4; *see* Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 14.
135 PDF of NASEM Report (Online Version) p. 220 (emphasis added).
136 PDF of NASEM Report (Online Version) p. 21 (emphasis added).
137 21 U.S.C. § 355(b)(1)(A); *see* Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 14.

In light of these inconsistencies, and the biases of the Committee members and review team as discussed above, it appears that the Committee's definition of clinical utility—invented solely for use in the NASEM Report in lieu of existing, accepted definitions set forth in academic literature—is a back-door attempt by the biased Committee to impose the ***same standards*** on cBHT that manufacturers must demonstrate to the FDA in order to commercialize a new drug: ***a process from which compounded products are statutorily exempt.***

The Studies Relied Upon by the Committee Do Not Reflect an Accurate or Complete Representation of cBHT

In its Study Scope, the Committee stated that it "maintained a prioritized focus" on cBHT preparations containing estradiol, estrone, estradiol cypionate, estriol, dehydroepiandrosterone ("DHEA"), pregnenolone, progesterone, testosterone, testosterone cypionate, and/or testosterone propionate, which it recognized as the "hormonal ingredients within the most commonly prescribed cBHT formulations."[138] To inform the Report, the Committee conducted two literature searches using keywords to identify peer-reviewed articles related to the safety, effectiveness, and clinical use of cBHT.[139] As set forth in Appendix B of the Report, the Committee identified:[140]

- **42** articles on progesterone;
- **34** articles on estradiol;
- **19** articles on estriol;
- **15** articles on estrone;
- **12** articles on testosterone;
- **3** articles on DHEA;
- **1** article on pregnenolone; and
- **1** article on testosterone propionate.

In addition to its own searches, the Committee commissioned three additional literature searches by the National Academies Research Center. The commissioned searches yielded 410 articles related to position statements on hormone therapy; nearly 6,000 legal documents (*e.g.*, federal and state cases, federal bills, law reviews) related to cBHT; and 62 dissertations/theses that could inform the Committee's understanding of the clinical use of cBHT.[141] The Committee also received hundreds of suggested articles and other references from study stakeholders, including the FDA, Professional Compounding Centers of America, representatives of select 503B outsourcing facilities, nonprofit professional organizations, and practicing medical prescribers of cBHT.[142]

The Committee summarily concluded that the vast body of studies, articles, theses, and reference documents collected were not "of adequate methodologic rigor for inclusion in its review."[143] Indeed, during its public briefing on the Report, Dr. Donald Mattison, NASEM's Committee Chairman for the Study, indicated that data submitted by top cBHT practitioners was not even considered:[144]

> **"The committee nixed evidence from those identified or shared by ad hoc participants or identified in public meetings."**

Ultimately, the Committee relied upon a total of 13 studies as the basis for its recommendations on the safety and effectiveness of cBHT, which are reflected in Table 7-1 of its Report.[145] In other words, out of the thousands of studies on cBHT submitted to the Committee, the Committee only relied upon 13—or less than 1%.

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138 PDF of NASEM Report (Online Version) p. 20.
139 PDF of NASEM Report (Online Version) p. 239.
140 PDF of NASEM Report (Online Version) p. 240.
141 PDF of NASEM Report (Online Version) p. 243.
142 PDF of NASEM Report (Online Version) p. 241 n.1.
143 PDF of NASEM Report (Online Version) p. 140.
144 Report Release Webinar: Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy," NASEM (Jul. 1, 2020), *available at* https://www.nationalacademies.org/event/07-01-2020/report-release-webinar-clinical-utility-of-treating-patients-with-compounded-bioidentical-hormone-replacement-therapy (timestamps 15:00 to 15:50).
145 PDF of NASEM Report (Online Version) pp. 142-149.

As an initial matter, NASEM's recommendations were drafted in view of only 13 studies that covered ***only five (5) different cBHT formulations***: eight (8) related exclusively to DHEA,[146] three (3) related exclusively to testosterone,[147] one (1) related exclusively to progesterone,[148] and one (1) examined the effects of a "bi-est" cream (estradiol and estriol) in combination with sublingual progesterone and testosterone perivaginal cream.[149] The Committee did not consider any studies on "bi-est" or "tri-est" combinations (estrone, estradiol, and estriol) alone, nor did it consider any studies on estradiol or estriol as standalone therapies. It also did not consider any studies on estrone, estradiol cypionate, pregnenolone, testosterone cypionate, or testosterone propionate. However, during its presentation to the NASEM Committee, one compounding pharmacy testified that it had compounded over ***149,000 unique hormone formulations using less than 10 hormones***.[150] In the Report, the Committee themselves recognized that the list of cBHT preparations they compiled "presents only a small sample of the universe of cBHT preparations and at best provides a snapshot and limited description of available cBHT preparations."[151] As such, the studies chosen by the Committee could not have been representative of the thousands of possible cBHT variations that could be used to treat patients.

Given that the majority of articles considered by the Committee relate exclusively to DHEA, one would assume that DHEA is the hormone most widely used by people in the U.S. However, the Committee's focus on DHEA is inconsistent with the data on the use of cBHT reviewed by the Committee itself, as set forth below:

- To identify trends in the use of cBHT, the Committee requested unpublished national data from the Nurses' Health Study 2 ("NHS2"), an ongoing, large, prospective cohort study on the lifestyles and health status of U.S. women.[152] According to the data collected in 2015, the most commonly reported bioidentical hormones were a combination of estrogen and progesterone (26%); a combination of estrogen, progesterone, and testosterone (25%); and testosterone alone (22%).[153]
- To understand the common types of cBHT preparations used by patients, 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.[154] The data showed that testosterone was prepared most frequently, followed by estradiol, testosterone cypionate, progesterone, and estriol.[155] Estrone, pregnenolone, and DHEA were only compounded in small quantities.[156]
- The Committee also submitted a data request to NABP. From its 2016 to 2018 pharmacy inspection application requests, NABP submitted a compiled list of the five most dispensed/distributed formulations from both 503A pharmacies and 503B outsourcing facilities.[157] The data from the 503A pharmacies showed that progesterone capsules and testosterone creams were dispensed most frequently, followed by estradiol/estriol and estradiol cream formulations.[158] The data from the 503B outsourcing facilities showed that progesterone capsules, testosterone pellets, and testosterone cypionate injections were the most commonly dispensed/distributed formulations.[159]

In light of the foregoing, it is evident that the majority of the articles selected by the Committee have little bearing on the question of whether cBHT is safe and effective for use, as the data on DHEA is not representative of the most commonly utilized therapies by patients in the U.S.

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146 Dahir, M., and D. Travers-Gustafson. Breast cancer, aromatase inhibitor therapy, and sexual functioning: A pilot study of the effects of vaginal testosterone therapy. The Journal of Sexual Medicine 2014;2(1):8–15; Jankowski, C. M., W. S. Gozansky, R. S. Schwartz, D. J. Dahl, J. M. Kittelson, S. M. Scott, R. E. Van Pelt, and W. M. Kohrt. Effects of dehydroepiandrosterone replacement therapy on bone mineral density in older adults: A randomized, controlled trial. The Journal of Clinical Endocrinology & Metabolism 2006;91(8):2986–2993; Kenny, A. M., R. S. Boxer, A. Kleppinger, J. Brindisi, R. Feinn, and J. A. Burleson. Dehydroepiandrosterone combined with exercise improves muscle strength and physical function in frail older women. Journal of the American Geriatrics Society 2010;58(9):1707–1714; Morales, A. J., R. H. Haubrich, J. Y. Hwang, H. Asakura, and S. S. Yen. The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women. Clinical Endocrinology 1998;49(4):421–432; Narkwichean, A., W. Maalouf, M. Baumgarten, L. Polanski, N. Raine-Fenning, B. Campbell, and K. Jayaprakasan. Efficacy of dehydroepiandrosterone (DHEA) to overcome the effect of ovarian ageing (ditto): A proof of principle double blinded randomized placebo controlled trial. European Journal of Obstetrics, Gynecology, and Reproductive Biology 2017;218:39–48; Panjari, M., R. J. Bell, F. Jane, J. Adams, C. Morrow, and S. R. Davis. The safety of 52 weeks of oral DHEA therapy for postmenopausal women. Maturitas 2009;63(3):240–245; Virkki, L. M., P. Porola, H. Forsblad-d'Elia, S. Valtysdottir, S. A. Solovieva, and Y. T. Konttinen. Dehydroepiandrosterone (DHEA) substitution treatment for severe fatigue in DHEA-deficient patients with primary Sjögren's syndrome. Arthritis Care & Research 2010;62(1):118–124; Wiser, A., O. Gonen, Y. Ghetler, T. Shavit, A. Berkovitz, and A. Shulman. Addition of dehydroepiandrosterone (DHEA) for poor-responder patients before and during IVF treatment improves the pregnancy rate: A randomized prospective study. Human Reproduction 2010;25(10):2496–2500.

147 Davis, S. R., P. J. Robinson, F. Jane, S. White, M. White, and R. J. Bell. Intravaginal testosterone improves sexual satisfaction and vaginal symptoms associated with aromatase inhibitors. The Journal of Clinical Endocrinology & Metabolism 2018;103(11):4146–4154; Glaser, R., A. E. York, and C. Dimitrakakis. Beneficial effects of testosterone therapy in women measured by the validated Menopause Rating Scale (MRS). Maturitas 2011;68(4):355–361; Witherby, S., J. Johnson, L. Demers, S. Mount, B. Littenberg, C. D. Maclean, M. Wood, and H. Muss. Topical testosterone for breast cancer patients with vaginal atrophy related to aromatase inhibitors: A phase I/II study. Oncologist 2011;16(4):424–431.

148 Leonetti, H. B., S. Longo, and J. N. Anasti. Transdermal progesterone cream for vasomotor symptoms and postmenopausal bone loss. Obstetrics & Gynecology 1999;94(2):225–228.

149 Mahmud, K. Natural hormone therapy for menopause. Gynecological Endocrinology 2010;26(2):81–85.

150 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 20.

151 PDF of NASEM Report (Online Version) p. 95.

152 PDF of NASEM Report (Online Version) p. 198.

153 PDF of NASEM Report (Online Version) p. 198.

154 PDF of NASEM Report (Online Version) p. 200.

155 PDF of NASEM Report (Online Version) p. 200.

156 PDF of NASEM Report (Online Version) p. 200.

157 PDF of NASEM Report (Online Version) pp. 200-201.

158 PDF of NASEM Report (Online Version) p. 201.

159 PDF of NASEM Report (Online Version) p. 201.

And despite its primary focus on DHEA—and its failure to consider any studies on estrone, estradiol cypionate, pregnenolone, testosterone cypionate, or testosterone propionate at all—the Committee nevertheless recommended that estradiol, estrone, estradiol cypionate, estriol, pregnenolone, progesterone, testosterone, testosterone cypionate, and testosterone propionate and all pellet cBHT therapies be considered candidates for the FDA "Difficult to Compound List."[160] Assessment of these compounds and formulations for inclusion on FDA's list of Difficult to Compound Drugs was outside of NASEM's commission scope—indeed, FDA was still working on a rule to address Difficult to Compound Drugs.[161] Yet, NASEM took it upon itself to recommend that these cBHT ingredients be included on the list.

To determine if a drug product should be added to the Difficult to Compound Drug list, the FDA considers whether the following characteristics "present a **demonstrable** difficulty for compounding that is **reasonably likely** to lead to an adverse effect on the safety or effectiveness of the drug product:"[162]

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

> Given that it did not consider ***any*** studies that speak to many of the hormones it recommended for the "Difficult to Compound" list, it is unclear how the Committee concluded that each of those hormones present a "**demonstrable** difficulty for compounding that is **reasonably likely**" to have an adverse effect. To the contrary, as noted by the Editor-in-Chief of the International Journal of Pharmaceutical Compounding, "cBHT formulations have been successfully compounded for decades and are not difficult to compound."[163]

With the exception of data on pellet therapies, the Committee provides little specifics about particular concerns with cBHT formulations other than concerns that generally apply to compounding—particle size, polymorphism, solubility, purity, in vivo metabolism, and formulation stability.[164]

In contrast to limited data provided by the Committee, compounding pharmacists in both Section 503A and 503B facilities have developed a large body of evidence to support the stability and utility of cBHT in various dosage forms, as described to the Committee during Hearing Testimony and in clinical literature.[165] This data and experience should be given more weight than the conjecture of concern.[166] Had the Committee visited a compounding pharmacy, as invited,[167] or reviewed the scientific literature provided, it would have gained additional insight on the characteristics at issue.

As part of assessing the difficulty of compounding, FDA often considers the compatibility and stability of active and inactive ingredients used in the formulation, as well as particle size and any potential concerns with maintaining particle size distribution that may impact the absorption and/or safety of the formulation.[168]

Compounding pharmacies have a long-standing history of compounding BHT therapies to address these issues. With respect to compatibility and stability of ingredients, compounding pharmacies have abundant evidence to support the stability and potency of cBHT. For example, several pharmacies provide beyond-use date data for cBHT formulations, which tests for potency, stability, and impurities.[169]

Addressing particle size is also routine practice for compounding pharmacists. There are many different techniques and equipment available to develop uniform particle size distribution. For example, there are three commonly used methods to reduce and achieve uniform particle size in compounded formulations—trituration, pulverization by intervention, and levigation.[170]

It does not appear that NASEM considered or evaluated how these issues have been addressed in clinical practice. NASEM provides little specifics to support a widespread concern with stability, potency, and/or particle size for any of the identified compounds used in cBHT preparation but discusses these issues in terms of a general concern expected for any compounded formulation and isolated incidences without support for broad concern.[171]

In sum, the Committee's narrow focus—both in terms of the quantity and substance of the data it considered—is not an accurate or complete representation of the BHT compounding that is occurring.

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160 PDF of NASEM Report (Online Version) p. 10.

161 Jane A. Axelrad, Understanding the List of Difficult to Compound Drug Products, Axelrad Solutions LLC (Jun. 27, 2019) p. 18-19.

162 *See* 78 Fed. Reg 72840 (emphasis added).

163 Allen LV, Jr., The NASEM cBHT Report, Part 1, International Journal of Pharmaceutical Compounding (Nov. Dec. 2020), p. 444.

164 PDF of NASEM Report (Online Version) p. 103.

165 *See, e.g.*, Statement of T.S. Wiley, Bio-Identical Hormones: Sound Science or Bad Medicine?, Senate Hearing 110-129 (Apr. 19, 2017), *available at* https://www.govinfo.gov/content/pkg/CHRG-110shrg37150/html/CHRG-110shrg37150.htm (last accessed Apr. 2, 2021).

166 PDF of NASEM Report (Online Version) p. 10.

167 *See, e.g.*, Email from AJ Day, PCCA, to Leigh Miles Jackson, NASEM, re: NASEM cost estimates (Aug. 21, 2019) (noting that one way to get information from the marketplace about cBHT "is to invite the committees to tour a compounding pharmacy, or a few pharmacies, to get a more thorough understanding of how they operate. I understand this may be challenging to organize, though it will undoubtedly give meaningful perspective to the conclusions the committees will reach.").

168 Jane A. Axelrad, Understanding the List of Difficult to Compound Drug Products, Axelrad Solutions LLC (Jun. 27, 2019) p. 12.

169 PCCA, FormulaPlus™ HRT Formulas, Formulas Subjected to Beyond-Use Date Testing.

170 The UNC School of Pharmacy Compounding Lab, Powders and Granules, available at https://pharmlabs.unc.edu/labs/powders/properties.htm (last accessed Apr. 2, 2021).

171 PDF of NASEM Report (Online Version) pp. 103-106.

The Standards for Evaluating the Safety and Efficacy of FDA-Approved Drugs Cannot Be Reasonably Applied to Highly Individualized Compounded Medications

Upon review of its 13 studies, the Committee concluded that "there is insufficient evidence to support the overall clinical utility" of cBHT because these preparations do not meet the safety and efficacy standards applied to FDA-approved drugs.[172] In support of its conclusion, the Committee cited, *inter alia*, the "paucity of reliable pharmacokinetic and bioavailability data for cBHT preparations as compared to FDA-approved drug products;" the "dearth of high-quality evidence—data from studies that would meet FDA's requirements for granting regulatory approval to a drug product;" and a lack of "well-designed and properly controlled clinical trials."[173] However, it is not reasonable or practical to apply the standards for FDA-approved drugs to cBHT formulations for a number of reasons.

First, as the Committee itself recognizes, compounding involves creating a medication "tailored to the needs of a patient."[174] The variability from person to person in the rate of absorption through the skin and mucus membrane, hormone metabolism, and sensitivity to administered hormones all lead to a nearly infinite variety of possible hormone therapies.[175] As a result, there are hundreds—if not thousands—of possible combinations, strengths, and dosage forms of the hormones used in BHT compounding.[176] However, drug development is a time-consuming process. Pursuant to the FD&C Act, drug companies must provide substantial evidence to the FDA that its new drug is both safe and effective before the drug can be marketed. Establishing safety and efficacy of a drug requires pharmaceutical companies to undertake lengthy and risky research and development ("R&D") processes. Overall, the development of a successful innovative product can take approximately 10 years, and the likelihood of receiving approval to market that product is estimated to be less than 12%.[177] To mandate that compounding pharmacies pursue FDA approval for each of the individualized therapies they provide on a daily basis would require them to anticipate a patient's needs nearly a decade in advance. In short, it is neither reasonable nor practical to apply the FDA standards for drug approval to compounded therapies, nor is it required or recommended by law.

The application of FDA drug approval standards to cBHT is equally unreasonable from a financial perspective. The development of a successful new drug costs a pharmaceutical company an average of $1.4 billion in out-of-pocket costs, and $2.6 billion in capitalized costs.[178] It is well-recognized that "long development times, scientific and regulatory uncertainties, and rising costs" of bringing a new drug to market has the potential to render biopharmaceutical innovation unsustainable.[179] Indeed, the pharmaceutical industry has experienced diminished productivity in recent years, as "[t]he return on investment for a typical biopharmaceutical portfolio today often will not even cover its cost of capital."[180] To address these challenges, pharmaceutical manufacturers either partner with larger, more established companies to jointly develop and commercialize their products or they turn to venture capital firms for funding. Thus, the availability of FDA-approved indications and products is necessarily dictated by manufacturers, who make economic determinations about the products to which they will dedicate their resources based upon the potential customer base and return on investment. As a practical matter, the individualized patient needs addressed by cBHT, by their very nature, do not provide the financial justification for the expenditures necessary to pursue FDA approval.

It is unreasonable to expect to see data on compounded therapies "from studies that would meet FDA's requirements for granting regulatory approval to a drug product" for the same reasons.[181] BHT compounding activities typically occur in small, regional, independently-owned pharmacies and the treatments vary in active ingredient and dosage strength based on the particular patient need. To conduct a comprehensive clinical trial in a centralized location would be financially prohibitive—no individual pharmacy would have the funds necessary. If independent pharmacies attempted to pool their resources and conduct the trial in tandem, it would be difficult, if not impossible, to achieve consistency in terms of study controls. And assuming, *arguendo*, that time and money were of no consequence, it is highly unlikely that any one particular combination, dosage form, and strength can be utilized by a large enough patient population to establish a sufficient patient base for a clinical trial.

Simply put, the dearth of "well-designed and properly controlled clinical trials" on cBHT is not attributable to laziness on the part of cBHT prescribers or a lack of evidence that cBHT is safe and effective—to the contrary, as discussed below, there is a body of evidence demonstrating consistent trends of positive efficacy with low instances of adverse events. Rather, the very nature of BHT compounding (and the patient needs it addresses) inhibits the reasonable application of FDA standards for drug approval to cBHT. In fact, the U.S. Supreme Court recognized as much in *Thompson v. Western States Medical Center*, wherein the majority stated that:[182]

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172 PDF of NASEM Report (Online Version) p. 9.
173 PDF of NASEM Report (Online Version) p. 220.
174 PDF of NASEM Report (Online Version) p. 2.
175 Daved Rosensweet MD, speaks before NASEM, The Menopause Method, *available at* https://vimeo.com/397476190.
176 Daved Rosensweet MD, speaks before NASEM, The Menopause Method, *available at* https://vimeo.com/397476190.
177 Biopharmaceutical Research & Development: The Process Behind New Medicines, PhRMA (2015), p. 1.
178 Biopharmaceutical Research & Development: The Process Behind New Medicines, PhRMA (2015), p. 1; DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. J Health Econ. 2016 May;47:20.
179 Strengthening Biopharmaceutical Innovation: The Growing Role of Corporate Venture Capital, Teconomy Partners LLC (Oct. 2018) p. 8.
180 Strengthening Biopharmaceutical Innovation: The Growing Role of Corporate Venture Capital, Teconomy Partners LLC (Oct. 2018) p. 8.
181 PDF of NASEM Report (Online Version) p. 220.
182 Thompson v. Western States Medical Center, 535 U.S. 357 (2002) (emphasis added).

> "Preserving the effectiveness and integrity of the FDCA's new drug approval process is clearly an important governmental interest, and the Government has every reason to want as many drugs as possible to be subject to that approval process. The Government also has an important interest, however, in permitting the continuation of the practice of compounding so that patients with particular needs may obtain medications suited to those needs. And **it 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.** Pharmacists do not make enough money from small-scale compounding to make safety and efficacy testing of their compounded drugs economically feasible, so **requiring such testing would force pharmacists to stop providing compounded drugs.** Given this, the Government needs to be able to draw a line between small-scale compounding and large-scale drug manufacturing."

In asserting that the evidence in support of BHT compounding should be evaluated against the same standards as FDA-approved medication, the Committee seeks to erase the line between compounding and drug manufacturing.

The Committee Relied Upon the 2002 Women's Health Initiative Study in Developing its Conclusions

The utility of cBHT was famously called into question after the publication of the results of the Women's Health Initiative ("WHI") Prempro study in 2002, which purported to show that hormone replacement therapy was harmful to women. Since then, criticisms of both the methodology and substantive findings in peer-reviewed publications have cast doubt on the reliability and utility of the study. In fact, some have argued that "the WHI hormonal replacement study had major design flaws that led to adverse conclusions about the positive effects of hormone therapy."[183] Despite the controversy surrounding the WHI Prempro study, the Committee relied upon the flawed study in evaluating the safety and efficacy of cBHT and in developing its conclusions.[184]

In the 1990s, the National Institute of Health launched the Women's Health Initiative ("WHI") studies to examine the effects of two FDA-approved drugs, Prempro (estrogen and progestin,[185] or "E+P") and Premarin (estrogen alone), in postmenopausal women. Premarin was a drug developed and commercialized by Wyeth, as described above. In July 2002, the WHI announced that the Prempro study was being terminated ahead of schedule due to adverse effects in the women receiving the drugs compared with those receiving a placebo, such as increased risk of breast cancer, coronary heart disease ("CHD"), stroke, and venous thromboembolism.[186] Although the study examined the effects of a single FDA-approved E+P drug on women who still had a uterus, the findings of the study were generalized to *all* varieties of hormone replacement therapy—including estrogen alone—in *all* women, including those whose uterus had been removed.[187] This announcement led to panicked headlines from the media, which resulted in an immediate and lasting negative effect on the perception and use of hormone replacement therapy around the world.[188] For example, within 18 months of the announcement, **half** of the women using hormone therapy in the United States stopped treatment.[189]

Since then, the WHI Prempro study—including the design, statistical analyses, and outcomes—has been criticized for a number of reasons. One study pointed out that 73% of the women in the Prempro study with a uterus had never previously received any form of hormone therapy, and that only 33% of the women given the drug were younger than 60—because the majority of women had 10 to 29 years of postmenopausal estrogen deficiency before beginning treatment with Prempro, it is likely that a large number of the study participants had already developed arteriosclerosis *before* receiving hormone therapy.[190] Given that aging women whose arteries may have plaques have been shown to react adversely to estrogen treatment, it is likely that the results of the WHI study were skewed.[191]

Another study examined the apparent spike in the risk ratio for breast cancer in the Prempro group compared to placebo. The study found that although observations of breast cancer for the Prempro group were higher than the placebo group during the 4th and 5th years of observation, detection levels for the two groups reconverged by the 6th year of observation.[192] The study concluded that it is therefore highly unlikely that this spike in risk ratio is predictive, especially considering that four of the six observation periods yielded risk ratio values at the no-effect level.[193] In addition, some clinicians expressed concern that the conclusions drawn from the data regarding the risk of CHD and breast cancer did not meet the usual criteria for statistical significance, and that the "short duration of the study makes it unlikely that the cancers were formed after therapy was started."[194] Other clinicians noted that the "significant" unblinding of the treatment group and the high drop-out rate likely compromised the results of the Prempro study.[195]

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183 Edward L. Klaiber et al., A Critique of the Women's Health Initiative Hormone Therapy Study. Fertility & Sterility, 2005;84:1589-1590.

184 *See* PDF of NASEM Report (Online Version), *in passim*.

185 Note that the study included progestin, not progesterone, which is commonly used in cBHT formulations. As such, the scope of these studies applicability to cBHT is limited.

186 Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3):321-33.

187 Sarrel PM, Njike VY, Vinante V, Katz DL. The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years. Am J Public Health. 2013;103(9):1583.

188 Burger HG, MacLennan AH, Huang KE, Castelo-Branco C. Evidence-based assessment of the impact of the WHI on women's health. Climacteric. 2012;15(3):281-87.

189 Burger HG, MacLennan AH, Huang KE, Castelo-Branco C. Evidence-based assessment of the impact of the WHI on women's health. Climacteric. 2012;15(3):281-87.

190 Klaiber EL, et al., A Critique of the Women's Health Initiative Hormone Therapy Study. Fertility & Sterility, 2005;84:1589-1590.

191 Klaiber EL, et al., A Critique of the Women's Health Initiative Hormone Therapy Study. Fertility & Sterility, 2005;84:1589-1590.

192 Clark JH. A critique of Women's Health Initiative Studies (2002-2006). Nucl Recept Signal. 2006 Oct 30;4.

193 Clark JH. A critique of Women's Health Initiative Studies (2002-2006). Nucl Recept Signal. 2006 Oct 30;4.

194 Goodman, N, Goldzieher J, Ayala C. Critique of the Report from the Writing Group of the WHI. Menopausal Med 2003;10:1–4.

195 *See* Klaiber EL, et al., A Critique of the Women's Health Initiative Hormone Therapy Study. Fertility & Sterility, 2005;84:1596; Clark JH. A critique of Women's Health Initiative Studies (2002-2006). Nucl Recept Signal. 2006 Oct 30;4.

Despite that both the methodology and the findings of the WHI Prempro study are contested at best—and debunked at worst[196]—the Committee nevertheless relied upon the flawed study in evaluating the safety and efficacy of hormone therapy and ignored the positive data on cBHT, as discussed below.

The Committee Ignored the Body of Evidence Demonstrating the Safety and Efficacy of cBHT

While compounding does not lend itself to widespread clinical trials, studies have been conducted which demonstrate that cBHT is safe and effective. However, in addition to citing the flawed WHI study in the Report, the Committee chose not to consider the body of evidence that demonstrates the safety and efficacy of hormone therapy—which was submitted to the Committee by industry stakeholders—and omitted the attendant data from its Report. As a result of this omission, the Report does not reflect an accurate or complete representation of the available data on the safety and efficacy of cBHT. For example, studies have shown that:

- Over a six-month period, women who took oral estriol compounded at dosages of 2mg, 4mg, 6mg, and 8mg per day, respectively, all saw improvement in menopausal symptoms.[197]
- Menopausal women who were given a compounded estradiol-progesterone formulation experienced significant improvement in menopause symptoms, compared to women who were given a commercially-manufactured estrogen formulation.[198]
- Postmenopausal women who had hysterectomies experienced increased bone mineral density in the lumbar spine after being treated with compounded estriol gel at a dose of 1.5mg daily.[199] Conversely, women who were given a placebo gel with a 2mg estriol tablet daily experienced ***decreased*** bone density.[200]

Similarly, the Committee ignored studies that demonstrated the safety of cBHT, and data comparing the safety of cBHT to synthetic HRT. For example:

- Adult traumatic brain injury patients who were administered compounded progesterone in the ER had a lower 30-day mortality rate than those who received no progesterone.[201]
- Compared to women who never used hormone replacement therapy, estriol users did not have an increased risk of breast cancer.[202] Among users of synthetic hormone replacement therapies, the risk of breast cancer doubled in comparison to women who never used hormone replacement therapy and estriol users.

In addition to the academic studies ignored by the Committee, the Committee also chose to disregard the testimony of various experts who presented their rationale, rooted in scientific research, for treating their patients with cBHT.[203] Nearly 20 physicians submitted statements to NASEM regarding their regular practice of treating patients with cBHT for a variety of medical conditions, based on their ***experience*** and sound medical opinion.[204] According to these physicians, cBHT has therapeutic effects in other areas including, *inter alia*, reducing the risk of Alzheimer's Disease;[205] improving cognitive function[206] and metabolic control of diabetes;[207] and alleviating psychological disorders such as depression and anxiety.[208] Additional highlights from these statements are set forth below.

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196 *See* Manson JE, et al. Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality, The Women's Health Initiative Randomized Trials. JAMA, 2017;318(10):927-938 (concluding in an observational follow up that women taking conjugated equine estrogens plus medroxyprogesterone acetate or conjugated equine estrogens alone in two randomized clinical trials between 1993 and 1998 was not associated with risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years)

197 Tzingounis VA, Aksu MF, Greenblatt RB. Estriol in the Management of Menopause. JAMA, 1978;236(16):1638-1641.

198 Hargrove JT, Maxson WS, Wentz AC, Burnett LS. Menopausal hormone replacement therapy with continuous daily oral micronized estradiol and progesterone. Obstetrics & Gynecology,1989;73(4):606-612

199 Devogelaer JP, Lecart C, Dupret P, De Nayer P, Nagant De Deuxchaisnes C. Long-term effects of percutaneous estriol on bone loss and bone metabolism in postmenopausal hysterectomized women. Maturitas, 1998;28:243-249.

200 Devogelaer JP, Lecart C, Dupret P, De Nayer P, Nagant De Deuxchaisnes C. Long-term effects of percutaneous estriol on bone loss and bone metabolism in postmenopausal hysterectomized women. Maturitas, 1998;28:243-249.

201 Wright DW, Kellermann AL, Hertzberg VS, et al. ProTECT: a randomized clinical trial of progesterone for acute traumatic brain injury. Annals of Emergency Medicine. 2007;49(4):391-402.

202 Bakken, K., Alsaker, E., Eggen, A.E. and Lund, E., Hormone replacement therapy and incidence of hormone-dependent cancers in the Norwegian Women and Cancer study. Int. J. Cancer, 2004;112:130-134.

203 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 20.

204 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 20.

205 *See, e.g.*, Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), Exhibit 1-H: Statement from Arlene Jean Jacobs, M.D., p. 112; Exhibit 1-K: Statement from Dr. John Joseph Peet, MD, FACOG, p. 132.

206 *See, e.g.*, Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), Exhibit 1-K: Statement from Dr. John Joseph Peet, MD, FACOG, p. 132.

207 *See, e.g.*, Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), Exhibit 1-M: Statement from Cory Stephen Rice, DO, p. 145.

208 *See, e.g.*, Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), Exhibit 1-K: Statement from Dr. John Joseph Peet, MD, FACOG, p. 133; Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), Exhibit 1-M: Statement from Cory Stephen Rice, DO p.145; Exhibit 1-N: Statement from Ann Elizabeth Stranger, MD, p. 151.

- Dr. Daniel Elias Melville, M.D., a member of the National Speaker Bureau for Bale Doneen Cardiovascular Prevention Method, prescribes cBHT as "a component of a prevention strategy for heart attack, stroke, and dementia."[209] Specifically referencing the cardiovascular system, he noted that "hormone optimization increases HDL, decreases LDL, smooths and dilates blood vessels so perfusion improves, and decreases free radicals, which ultimately can damage arteries and other healthy tissue (which is the primary cause of Alzheimer's dementia)."[210]
- Dr. John Joseph Peet, M.D, FACOG, a physician who has received multiple research-based awards throughout his career,[211] explained that he has been prescribing hormone therapy for over 20 years and cBHT, specifically, for 10 years.[212] Notably, he pointed out that, at the time, he had over 5,000 patients being treated with cBHT, and "Approximately 90-95% of my male and female patients treated with some form or combination of compounded BHRT ***have their symptoms completely resolved***."[213] Dr. Peet further describes that improvements in symptoms is important for patients to continue with their prescribed treatment plans.[214]
- Dr Arlene Jean Jacobs, M.D. is an OB/GYN who has received a multitude of awards and honors in her field, including one of America's Top Obstetricians & Gynecologists in 2015, 2016, and 2017.[215] Her statement to NASEM asserted that she uses cBHT, in comparison to commercially available hormone therapy, because "there are not enough dosage forms and strengths of commercially available BHRT to treat the idiosyncratic nature of hormones" and they provide the "ability to adjust and optimize the patient's medication dosages rather than relegating my patients to cookie cutter, commercially available medication that does not work for them." [216]

In sum, large scale clinical trials are unworkable for cBHT due to the highly individualized nature of hormone treatment and lack of a sufficient patient population for a trial. Nevertheless, ample data—and real-world experiences of the physicians who prescribe cBHT products every day—exists that shows consistent trends of positive efficacy with low instances of adverse events for cBHT. While no study on its own is sufficient and all have limitations, the totality of this evidence reveals incontrovertible positive trends with no significant signals of negative safety outcomes. This data, in addition to the widespread clinical use of cBHT with successful patient outcomes outlined throughout this white paper, demonstrates the clinical utility of CBHT.

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209 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 126.

210 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 126.

211 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 138.

212 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), pp. 132, 139.

213 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p.p. 132-133 (emphasis added).

214 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 134.

215 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 114.

216 Reed Smith, Public Comment to FDA Regarding the National Academies of Sciences, Engineering, and Medicine Report on the Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy" (published Mar. 11, 2021), p. 113.

The Committee's Recommendations, if Implemented, Would Harm Patients Across the United States and Their Prescribers' Ability to Care for Them

The Committee itself recognizes that "millions of men and women have reported using compounded hormone therapy."[217] However, if implemented, the Committee's recommendations would deprive these patients from getting the treatment they need and would render patients unable to combat life-altering symptoms that are currently managed through compounded hormone therapy.

In addition to the detrimental effect on current cBHT patients, the Committee's recommendations would have ramifications for potential patients as well. Wide acceptance of the NASEM Report—which positions cBHT as an unsubstantiated therapy with little clinical utility—may discourage prescribers and patients from considering hormone therapy as a viable treatment option in the future. This would have disastrous effects, as evidenced by peer-reviewed studies submitted to the Committee during the literature review process.

For example, a study funded by the Center for Disease Control and Prevention ("CDC") examined the effect of estrogen avoidance on mortality rates among hysterectomized women aged 50 to 59, following the 2002 WHI publication which was understood to show that hormone replacement therapy was harmful to women.[218] Despite that both the WHI's methodology and substantive findings were later disputed, prescriptions for all forms of hormone therapy in hysterectomized women had declined by nearly 80% in the period from 2002 to 2011.[219] Published in the American Journal of Health in 2013, the CDC study determined that the avoidance of estrogen therapy by prescribers and patients **caused the premature death of anywhere between 50,000 and 91,000 postmenopausal women** aged 50 to 59 since the WHI report was released in 2002.[220] Similar to the WHI report, the NASEM Report appears to attempt to spread fear of cBHT, despite a lack of specific articulated risks. And just as the WHI report caused patients to shy away from estrogen to their detriment, the fearmongering by the Committee will cause harm to patients as well.

Acceptance of the NASEM Report recommendations would not only have detrimental effects on patient health and well-being, but it would also enable the FDA to expand its powers beyond those granted to it by the U.S. government and intrude into the sacred physician-patient relationship. As described at the outset of this Report, it is the moral duty of a physician to use sound medical judgement to alleviate suffering for his or her patients.[221] A physician must maintain clinical decision-making authority to judge what is best for each individual patient, given that patients often have variations in their clinical histories and the best form of treatment for one patient may not be suitable for another with the same exact condition.[222] To protect the discretion of prescribers and the wellbeing of patients, U.S. law grants physicians the right to fulfill their duty to patients without regulatory intervention from the FDA.[223] However, the recommendations of the Committee are antithetical to this right and directly interfere with the ability of physicians to meet patients' needs through individualized treatment decisions.

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217 PDF of NASEM Report (Online Version) p. 1.

218 Sarrel PM, Njike VY, Vinante V, Katz DL. The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years. Am J Public Health. 2013;103(9):1583.

219 Sarrel PM, Njike VY, Vinante V, Katz DL. The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years. Am J Public Health. 2013;103(9):1583.

220 Sarrel PM, Njike VY, Vinante V, Katz DL. The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years. Am J Public Health. 2013;103(9):1583-84.

221 Patient-Physician Relationships: Code of Medical Ethics Opinion 1.1.1., American Medical Association, *available at* www.ama-assn.org/delivering-care/ethics/patient-physician-relationships (last accessed Apr. 2, 2021).

222 Handbook Addendum – Supplemental Business and Information, American Medical Association (Oct. 30, 2020), *available at* https://www.ama-assn.org/system/files/2020-10/nov20-handbook-addendum.pdf;W (last accessed Apr. 2, 2021); Wendy Teo. FDA and the Practice of Medicine. Seton Hall Legislative journal. 2017;2(41):305, 309.

223 *See* 21 U.S.C. § 396.

Conclusion

As detailed throughout this white paper, cBHT is used for a variety of medically necessary reasons by patients across the U.S. Continued access to cBHT is critical to patient health and well-being.

While there are opportunities for improving BHT compounding practices, such as establishing clearer guidelines for patient monitoring, the NASEM Report does not provide an accurate or complete lens through which these opportunities can be evaluated. Rather, the NASEM Report offers a biased perspective of cBHT, promulgated by a Committee with practically no patient-facing experience with hormone therapy and guided by a regulatory body with a clear interest in either bringing compounding under its purview or effectively prohibiting the practice of cBHT altogether.

Moreover, as a practical matter, it is unlikely that the concerns of the FDA and those in opposition to cBHT will be addressed through the implementation of the Committee's recommendations. Most physicians and pharmacists—like any other professional—understand that it is in their *own* best interest to offer the best possible care to patients as a practical matter. To do otherwise would result in both financial and reputational loss, as it would be in violation of their professional oaths and could have significant ramifications (*e.g.*, the loss of their professional licensure). Laws at the state and federal level mitigate the risk of improper or dangerous business practices. State boards of medicine and pharmacy establish requirements and guidelines for safely treating patients and compounding treatments, respectively. While it may be tempting to seek to regulate every aspect of the health care continuum, it is important to recognize that there will always be bad actors. Try as it might, the FDA cannot prevent individuals from committing a crime or unintentionally causing harm. However, if the Committee's recommendations are implemented, the FDA will adversely affect the safe practice of medicine and the well-being of cBHT patients nationwide.

In sum, NASEM's recommendations seek to severely restrict—or eliminate entirely—the ability of the physician to prescribe cBHT to his or her patients. In turn, the restriction on the physician's ability to prescribe cBHT would limit the patient's choices for treatment. When a patient's choices are limited, so too is his or her path to wellness.

We therefore recommend that patient need must take priority over policy-making.

We recommend that FDA not rely on or consider the NASEM Report and instead work to ensure that prescribers, patients, and pharmacists may continue to collaborate on treatment options that work best for the individual patient in a manner that is safe and effective. More specifically, we recommend that:

1. FDA should work collaboratively with medical and pharmacy compounding industries to address concerns around labeling and adverse event reporting for compounded therapies.
    a. Developing a system in which patients are consistently provided with information specific to their prescription medication should be encouraged, including developing product monographs for ingredients used in compounded treatments. The system should ensure that patients receive up-to-date, accurate, and consistent information about their prescription medications.
    b. The current adverse event reporting system and process should be evaluated for improvements to ensure compounded therapies are being addressed. Improvements to this system, if necessary, should broadly address concerns with cBHT and other compounded therapies.
2. FDA should sponsor or encourage sponsorship of educational campaigns directed to medical providers, pharmacists and/or patients focusing on the benefits and risks of cBHT compared to commercially available hormone therapies. Such educational programs should provide fair-balanced benefit and risk information in a manner that is respectful of the doctor-patient relationship.
3. FDA should develop and/or improve upon systems to encourage adherence to Code of Ethics for prescribers and pharmacists. Appropriate use of cBHT should be encouraged. Patients are not served if cBHT is not being appropriately used (*i.e.*, overuse and/or underuse).
4. Compounding pharmacies should be expected to comply with USP Standards related to the preparation of compounded prescriptions. State Boards of Pharmacy should assess their current requirements and monitoring and enforcement efforts around compliance with USP Standards.

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