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REVIEW ARTICLE

Update on medical and regulatory issues pertaining to compounded and FDA-approved drugs, including hormone therapy

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Abstract

Objective: We review the historical regulation of drug compounding, concerns about widespread use of non-Food and Drug Administration (FDA)-approved compounded bioidentical hormone therapies (CBHTs), which do not have proper labeling and warnings, and anticipated impact of the 2013 Drug Quality and Security Act (DQSA) on compounding.

Methods: US government websites were searched for documents concerning drug compounding regulation and oversight from 1938 (passage of Federal Food, Drug, and Cosmetic Act [FDCA]) through 2014, including chronologies, Congressional testimony, FDA guidelines and enforcements, and reports. The FDCA and DQSA were reviewed. PubMed and Google were searched for articles on compounded drugs, including CBHT.

Results: Congress explicitly granted the FDA limited oversight of compounded drugs in a 1997 amendment to the FDCA, but the FDA has encountered obstacles in exercising that authority. After 64 patient deaths and 750 adversely affected patients from the 2012 meningitis outbreak due to contaminated compounded steroid injections, Congress passed the DQSA, authorizing the FDA to create a voluntary registration for facilities that manufacture and distribute sterile compounded drugs in bulk and reinforcing FDCA regulations for traditional compounding. Given history and current environment, concerns remain about CBHT product regulation and their lack of safety and efficacy data.

Conclusions: The DQSA and its reinforcement of §503A of the FDCA solidifies FDA authority to enforce FDCA provisions against compounders of CBHT. The new law may improve compliance and accreditation by the compounding industry; support state and FDA oversight; and prevent the distribution of misbranded, adulterated, or inconsistently compounded medications, and false and misleading claims, thus reducing public health risk.

Key Words: Bioidentical hormone therapy – Compounded drugs – Estrogen therapy – Menopause – Progesterone – Review.

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The role of the US Food and Drug Administration (FDA) in reviewing the safety and effectiveness of a new drug before approving it for human use is so widely known that prescribers and users may assume all prescribed drugs are subject to the same process. Compounded drugs, however, are not evaluated and approved by the FDA. A compounded drug is a customized medication prepared by a physician or pharmacist with a prescription for someone who has a medical concern precluding him or her from using a similar FDA-approved product or who needs an approved drug in an unavailable formulation.[1,2] Hospitals sometimes purchase compounded drugs when FDA-approved medications are in short supply,[1] which may not always be consistent with physicians' knowledge and approval.

Determining the extent of drug compounding in the United States is difficult. Federal regulations do not require compounders to register with the FDA or report sales.[3] In October

2012, the International Academy of Compounding Pharmacists estimated that more than 25,000 US pharmacies engaged in basic drug compounding, at least 7,500 performed advanced (sterile) compounding, and approximately 3% of the 4 billion prescriptions filled annually in the United States were for compounded drugs.[4,5] Custom-compounded bioidentical hormone therapy (CBHT), primarily consisting of estrogen and progesterone combinations, has grown tremendously.[3] A recent study reported that up to 1 to 2.5 million US women use CHT annually at an estimated annual cost of $1 to $2 billion.[6]

Because compounded drugs like CBHT were custom-made for individual users by different pharmacies using different processes and ingredients, requiring compounders to evaluate the safety and efficacy of each unique formulation in clinical trials or to seek federal approval was considered impractical.[7] Over the past few decades, however, drug compounding evolved beyond the local pharmacist to include manufacturers compounding medications in batches and shipping them across state lines.[1,8-12] Legislators, regulators, healthcare professionals, and other stakeholders became concerned about the widespread use of unapproved medications—whether mass distributed or individually dispensed—that did not meet the same federal standards for efficacy, safety, and manufacturing as FDA-approved medications.[8,9] After several safety incidents attributed to compounded drugs,[13-17] culminating with 64 fatalities in 2012 from tainted methylprednisolone acetate injections compounded at a single facility,[18] Congress passed the 2013 Drug Quality Security Act (DQSA).[19] Title 1 of the DQSA (the Compounding Quality Act [CQA]) expands the FDA's authority to regulate compounding facilities and reinforces its authority over traditional compounding under the Federal Food, Drug, and Cosmetics Act (FDCA).[19]

This review article's objectives are to provide historical context for enactment of the CQA, compare regulatory requirements for drug compounders versus manufacturers of FDA-approved drugs, and examine possible effects of the CQA on the drug compounding industry. We will also discuss safety and efficacy issues associated with CBHT and implications of the CQA for CBHT providers and users. Table 1 provides a glossary of abbreviations used in the review.

TABLE 1. *Glossary of abbreviations*

Abbreviation	Definition
API	Active product ingredients
CBHT	Compounded bioidentical hormone therapy
CDER	Center for Drug Evaluation and Research
CHT	Compounded hormone therapy
CQA	Compounding Quality Act (Title 1 of the DQSA)
DQSA	Drug Quality Security Act (2013)
EPT	Combined estrogen and progestogen therapy
FDA	US Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act (1997)
FDCA	Federal Food, Drug, and Cosmetics Act (1938)
GMP	Good Manufacturing Practices
HT	Hormone therapy
IND	Investigational New Drug
NDA	New drug application
RCT	Randomized controlled trials
SPB	State pharmacy board
USP	United States Pharmacopoeia
VMS	Vasomotor symptoms
VVA	Vulvar and vaginal atrophy

SUMMARY OF THE GENERAL DRUG APPROVAL PROCESS

The FDA requires pharmaceutical companies to establish the safety and efficacy of a drug candidate and seek approval of a drug before marketing it in the United States. The approval process for a new molecular entity is lengthy, rigorous, and expensive and typically begins with in vitro and animal testing to show the agent is active and unlikely to be toxic to humans.[20,21] The sponsor then files an Investigational New Drug (IND) application explaining the preclinical findings and requesting permission to conduct human clinical trials.[22,23]

Early clinical trials are typically designed to determine the drug's pharmacokinetic properties and identify acute safety issues in a small number of healthy volunteers.[20,23,24] Subsequent trials may test for dose response or provide preliminary data on efficacy and safety in the targeted population.[20,24] Pivotal phase 3 trials are randomized controlled trials (RCTs) comparing the safety and efficacy of a new drug with placebo or another standard treatment and may recruit hundreds to thousands of participants.[24,25] All study protocols must meet standards of the FDA and an Institutional Review Board or similar FDA-registered group.[20,26]

The FDA has additional guidance specific to different drug classes or patient groups.[21,27] The guidance for trials evaluating hormone therapy (HT) for indications of vasomotor symptoms (VMS) and vulvar vaginal atrophy (VVA) include specific eligibility criteria and safety and efficacy endpoints (Table 2).[27] For example, for combined estrogen and progestogen therapy (EPT), the FDA requires a 12-month, phase 3, double-blind, dose-ranging RCT to assess efficacy for reducing the number and severity of hot flushes and endometrial safety.[27] For a new molecular HT entity, the FDA requires two placebo-controlled phase 3 trials.[27]

Depending on clinical trial outcomes, the sponsor may file a New Drug Application (NDA), reporting all study results (safety, efficacy, and pharmacokinetic data); describing the manufacturing process and methods used to ensure the purity, potency, and quality of the drug; and proposing label and package-insert language.[25] The FDA provides guidelines on labeling HT products to ensure adequate disclosure of their class-based risks.[28]

The FDA considers the data and the drug's risk-benefit profile, inspects the manufacturing facility and process for adherence to current Good Manufacturing Practices (GMP), and reviews labeling and product inserts.[20,25] With drug approval, the sponsor conducts postmarketing surveillance and submits regular updates on potential safety issues.[20,25]

THE FDA'S EVOLVING APPROACH TO DRUG COMPOUNDING

Compounding is the "combining, admixing, mixing, diluting, pooling, reconstituting, or otherwise altering of a drug or

TABLE 2. *Safety and efficacy guidelines from the FDA for trials of hormone therapy*[27]

Protocol recommendations	Efficacy considerations[a]	Safety considerations
Dose-ranging studies prior to phase 3 development	Co-primary endpoint for VMS consists of mean changes at 4 and 12 weeks in Frequency of VMS Severity of VMS	Changes in lipid, carbohydrate, and coagulation parameters[a]
≥One randomized phase 3 trial Placebo-controlled Double-blind 12-Week duration Including ineffective dose	Co-primary endpoint for VVA consists of mean changes at 12 weeks in Most bothersome symptom Vaginal pH VMI (% change in parabasal and superficial cells)	Serum levels of parent compounds and metabolites
Eligibility Postmenopausal women Negative mammogram in women aged ≥40 y A uterus for trials evaluating EPT Negative endometrial biopsy results for women with a uterus		New findings during physical examination, including breast changes Endometrial biopsy results for women with on-study uterine bleeding For EPT trials, 12-month incidence of[b] Endometrial hyperplasia (target, <1%) Hyperplastic polyps and related atypia

EPT, estrogen and progestogen therapy; VMI, vaginal maturation index; VVA, vulvar-vaginal atrophy.
[a]All changes are to be measured from baseline.
[b]Slides must be evaluated separately by three independent pathology experts whose curricula vitae must be provided to the FDA.

bulk drug substance to create a drug."[19] Makers of compounded drugs (including CBHT) who comply with appropriate FDCA provisions are exempt from the rigorous drug approval process established for branded drugs.[20,22,29,30] Bioequivalency or pharmacokinetic studies are not required for compounded products.[30,31] Makers of nonsterile compounded drugs who operate within FDCA restrictions for traditional compounding are generally exempt from GMP and routine FDA inspection.[30,31] Thus, they have not been required to evaluate their customized drugs for purity, potency, or quality,[30,32] although many may choose to self-monitor or be accredited by the Pharmacy Compounding Accreditation Board,[33] a service of the Accreditation Commission for Health Care.[34] Compounded medications can also be dispensed without standardized labels, use instructions, or product inserts.[30,31] Whereas all FDA-approved HT products carry a boxed warning about the class-based risks of estrogens and progestogens, CBHT products—which contain these hormones—do not have this requirement.[28]

The FDCA

The FDCA was passed in 1938 (Fig. 1) after 100 people died from strep-throat treatment (Elixir of Sulfanilamide), one of many tragedies over the years due to insufficient regulatory oversight of medicinal products.[21] The FDCA fundamentally changed how drugs were developed and marketed in the United States. At the time it was enacted, drug compounding was considered an aspect of traditional pharmacy practice under state jurisdiction and the FDCA made no distinction between branded versus compounded drugs. However, the Act and its subsequent amendments endowed the FDA with broad authority to regulate all medical drugs and devices in the interest of protecting public health. Over the next 50 years,[35] the FDA rarely enforced FDCA provisions against pharmacies engaged in compounding drugs that, as modified versions of FDA-approved products, were de facto unapproved new drugs. Instead, the FDA focused on compounders believed to pose a major threat to public safety and deferred to state pharmacy boards (SPBs) for policing compounders who committed less serious violations.[35]

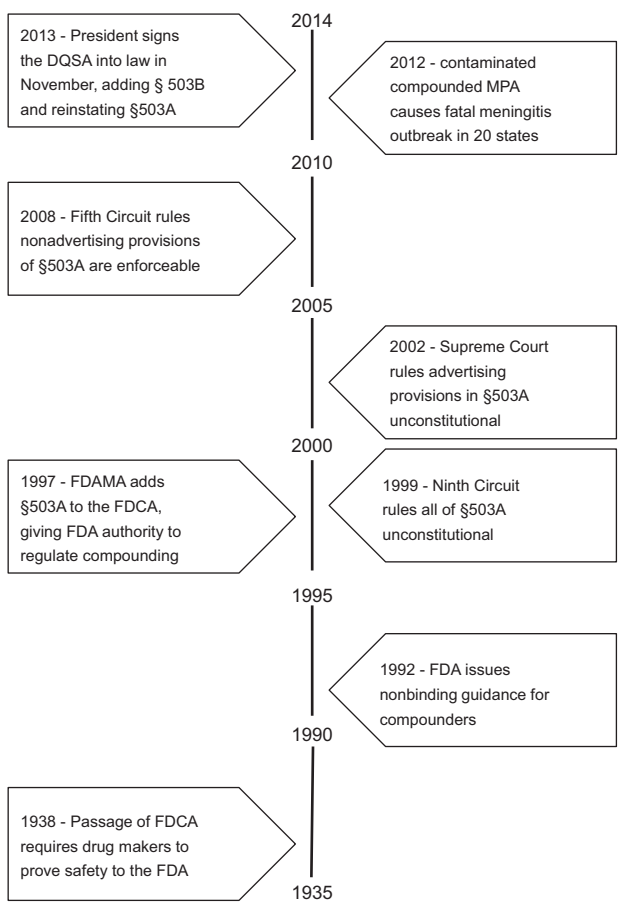

FIG. 1. Timeline of regulatory actions and events related to drug compounding in the United States.

The FDA modernization act (§503A)

The FDA's growing concern in the early 1990s that pharmacies "had begun producing drugs beyond what had historically been done with traditional compounding"[2] and that "some pharmacists were manufacturing and selling drugs under the guise of compounding"[35] to circumvent FDCA requirements, prompted the FDA to issue a Compliance Policy Guide in 1992 detailing plans for enforcing FDCA requirements against compounded drugs.[36] The 1992 guidance was withdrawn after Congress passed the Food and Drug Administration Modernization Act (FDAMA) in 1997, codifying the FDA's enforcement authority over compounding under the FDCA as §503A.[11,35,37]

Under FDAMA, licensed pharmacists engaged in traditional compounding were exempted from GMP; federal labeling standards; and NDA requirements, including safety and efficacy studies, if their compounded drugs met certain requirements.[30] They were not required to register with the FDA, undergo routine inspection, or report adverse events.[30] To qualify for these exemptions, compounders could not advertise or solicit prescriptions for compounded drugs, regularly reproduce copies of FDA-approved drugs, or compound drugs the FDA classified as unsafe.[11,37-39] Compounders had to use bulk substances or active product ingredients (APIs) for which a United States Pharmacopoeia (USP) or National Formula monograph existed and were prohibited from making products the FDA considered too complex to produce in the pharmacy setting.[30] In addition, FDAMA placed limits on a pharmacy's out-of-state compounded drug sales.[30] Although §503A formally codified and clarified the FDA's authority to regulate compounding, primary oversight remained with state pharmacy boards (SPBs).[30]

The compounding industry challenged FDAMA's prohibitions on advertising and solicitation, and conflicting opinions from US courts left enforceability of FDAMA unclear.[35,38,39] The Ninth Circuit Court of Appeals invalidated §503A in its entirety, whereas the US District Court of Nevada struck only the advertising provisions.[35,38,39] The FDA appealed to the Supreme Court, which ruled in 2002 that the advertising restrictions were unconstitutional; however, the court did not address FDAMA's remaining provisions.[35] Months later, the FDA issued another Compliance Policy Guide on compounding, which led to further challenges to the FDA's authority to regulate compounding[37] and disparate rulings that left the FDA with varying levels of enforcement authority by region.[37]

In 2005, Wyeth Pharmaceuticals, a maker of FDA-approved HT products, filed a Citizen Petition with the FDA to call attention to unregulated compounding practices.[40] Wyeth alleged that several compounding pharmacies were violating provisions of §503A, such as copying FDA-approved HT products; making unsupported claims about CBHT's safety and benefits, especially relative to FDA-approved HT; misbranding products; using unapproved hormones like estriol; and failing to use GMP.[40]

At a 2007 senate hearing on compounded drugs, then-director of the Center for Drug Evaluation and Research (CDER) Steven Galson acknowledged CBHT use was increasing and expressed concern that patients were being misled about CBHT's benefits.[37] He noted some compounders advertised CBHT products as superior to FDA-approved hormones despite the lack of scientific evidence and often neglected to inform patients and prescribers that approved and compounded HT likely carried similar risks.[37] Between 2007 and 2008, the FDA issued warning letters to seven pharmacies making CBHT and launched a public awareness campaign to correct misperceptions about CBHT.[13,14,41]

The CQA of 2013

The magnitude of risk to public health from unregulated compounded drugs became apparent in 2012 after contaminated methylprednisone acetate injections compounded at the New England Compounding Center caused a multistate outbreak of meningitis.[18] The final tally showed at least 13,500 patients in 20 states may have been exposed to the tainted steroid, resulting in 751 illnesses and 64 deaths.[18]

During congressional hearings on the outbreak, FDA officials said the FDA was hampered in regulating compounders by "ambiguous, fragmented, unclear, and contested authorities in this particular realm of pharmacy and drug manufacturing."[42] Janet Woodcock of the CDER explained that because compounders did not have to register with the FDA, "We don't know who they are, we don't know where they are, and we don't know what they are making."[2] Both officials told Congress the lack of mandatory reporting of adverse events associated with compounded drugs made it harder to identify potential health threats.[2,42]

In November 2013, Congress passed the DQSA, which strengthens the FDA's authority to regulate compounded pharmaceuticals under Title 1 (the CQA).[19,30] The primary actions of the CQA are to add §503B to the FDCA, which defines *outsourcing facilities* as a new class of sterile drug compounders distinct from traditional compounders; and strike prohibitions on advertising and soliciting from §503A adjudicated as violating free speech, thus recodifying the FDA's authority to regulate traditional compounding under FDAMA §503A.[2,19] The CQA clarifies the applicability of misbranding provisions in the FDCA to include false and misleading claims about compounded drugs.

Outsourcing facilities are companies permitted to compound sterile drugs (ie, for intravenous, intramuscular, subcutaneous, intradermal, intrathecal, ophthalmic, otic, intranasal, or pulmonary administration) even without a prescription.[43,44] Many are registered pharmacies that perform admixing and compounding of sterile drugs for hospitals. Traditional compounders are pharmacies that, as part of their practice, make customized medications prescribed for a patient with a medical need.

Table 3 summarizes how the amended FDCA applies to traditional compounders versus outsourcing facilities and compares this with regulatory requirements for manufacturers of FDA-approved drugs. Neither traditional compounders nor outsourcing facilities may compound drugs the FDA

TABLE 3. *Differences in federal regulations for drugs made by traditional compounders, registered outsourcing facilities, and commercial manufacturers*[19-23,25,26,30,31]

Regulation	Traditional compounders	Registered outsourcing facilities	Commercial manufacturers
Cannot make drugs the FDA considers unsafe or ineffective	X	X	X
Cannot make drugs that are complex or that use complex dosage forms	X	X	
Cannot introduce new drugs without premarket review or filing an NDA			X
Cannot reproduce large quantities of FDA-approved drugs	X	X[a]	NA
Cannot make false or misleading claims on labels or in ads	X	X	X
Must conduct clinical trials for safety and efficacy[b]			X
Must provide patients with detailed use instructions[b]			X
Must use bulk APIs that have a USP or National Formulary monograph; are used in an approved drug; are found on an FDA list	X	X	
Must package drugs with a label that accurately reports strength, quality, purity, and expiration			X
Must include drug name and "this is a compounded drug" on the label		X	
Must adhere to GMPs[c]		X	X
Must undergo federal inspection of the facility		X	X
Must report all transactions to the FDA every 6 mo		X	
Must investigate and report adverse events		X	X
Must be a state-licensed pharmacist or physician	X		NA
Production of compounded drugs requires a prescription	X[d]		NA
If not a licensed pharmacist or physician, must be supervised by one		X	
Can only compound-prescribed drugs for patients with a medical need	X		NA
May sell drugs out of state	X[e]	X	X

API, active product ingredient; FDA, Food and Drug Administration; GMP, Good Manufacturing Practices; NDA, New Drug Application; USP, United States Pharmacopoeia; X = required.

[a]Compounding facilities may compound approved drugs if a drug shortage has been confirmed.

[b]To be exempt from these provisions, a compounder must be compliant with the FDCA.

[c]Traditional compounders do not have to follow GMPs but must prepare drugs in a sanitary fashion.

[d]Traditional compounders may practice anticipatory compounding for a patient with a history of filling prescriptions for that drug at the facility.

[e]Traditional compounders can fill a limited number of out-of-state prescriptions (typically <5%, depending on state law).

considers unsafe or ineffective, introduce new drugs, manufacture large quantities of approved drugs absent a drug shortage, or compound complex medications or dosage forms.[19,30,31] All compounders must use components of FDA-approved drugs or APIs or bulk drug substances for which a USP or National Formulary monograph exists or that are included on a forthcoming FDA list.[30,31] Drugs must be packaged correctly and accurately labeled with the drug's strength, quality, and purity.[19,31] Compounders, like manufacturers of FDA-approved drugs, are barred from making false or misleading claims about their products.[19,30,31]

Because the law does not establish a nationwide tracking system for drug compounders, the FDA will largely depend on SPBs for notification of compounders who are not registered outsourcing facilities and are noncompliant with §503A.[3,45] The CQA requires the FDA to develop an electronic system to receive SPB communications.[19,45] The FDA plans to prioritize enforcement of compounding based on risk, devoting more resources to pharmacies with a history of unsafe sterile compounding.[31] Although the CQA is expected to improve the safety of some compounded drugs, it is not intended to hold compounded drugs to the same safety and efficacy standards as FDA-approved drugs.

OUTSOURCING FACILITIES

Under the CQA, compounders who plan to continue making sterile medications without prescriptions may voluntarily register with the FDA as an outsourcing facility.[31] The FDA inspects outsourcing facilities at registration and on a risk-needed basis thereafter for GMP compliance.[31] Although outsourcing facilities do not have to be licensed pharmacies, a licensed pharmacist or physician must supervise compounding.[19,46] Registered facilities compliant with GMP and other CQA provisions may ship unlimited quantities of compounded drugs across state lines. They will remain exempt from having to meet strict labeling requirements,[2,19,39] conducting safety and efficacy trials, and submitting products for FDA approval. They must regularly report all transactions and serious, unexpected adverse events to the FDA.[19,45] Compounders who do not qualify as traditional compounders under §503A yet decline to register as an outsourcing facility under §503B will be regarded as commercial drug manufacturers and are expected to file an IND application for any drug noncompliant with §503A.[46] Otherwise, the FDA may seize their products or issue injuctions.[46] To encourage large-scale compounders of sterile drugs to register, the FDA is urging hospitals and other drug purchasers to adopt policies requiring sterile compounded drugs to be purchased from registered outsourcing facilities.[39]

TRADITIONAL DRUG COMPOUNDERS

Physicians and pharmacists who practice traditional compounding and wish to remain exempt from FDA approval requirements for new drugs, GMP, and labeling requirements for safe use must meet conditions laid out in §503A. They require licenses and can only compound medications "based on the receipt of a valid prescription order, or a notation,

approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient."[31] Traditional compounders are permitted to compound "limited quantities" of medications for prescriptions for established patients.[31]

In July 2014, the FDA issued guidance for traditional compounders that limits their interstate transactions to 5% or less of total prescriptions unless the FDA has a memorandum of understanding with the compounder's state.[31] The SPBs will retain primary responsibility for regulating traditional compounding.[31,39,46] However, should the FDA determine a compounded drug violates §503A, possible penalties include warning letters, product seizures, injunctions, or prosecution.[47] The extent to which reinstatement of §503A will affect traditional compounding is expected to become clearer once the FDA publishes its final lists of bulk drug substances, drugs that present demonstrable difficulty in compounding, and unsafe or ineffective drugs not permitted to be compounded.[47]

SAFETY AND QUALITY CONCERNS WITH COMPOUNDED DRUGS

Since the 2012 meningitis outbreak, the FDA has documented 20 compounders who shipped contaminated drugs, 125 patients who experienced serious adverse events, and more than 150 compounded products recalled because of contamination.[2,48] Of the more than 60 sterile compounding facilities the FDA inspected, almost none were GMP compliant.[2,49] Reported violations include failure to maintain sanitary conditions, failure to conduct endotoxin and sterility tests or calibrate equipment, and storing expired and unexpired products together.[2,50,51]

According to Staes et al,[15] sterile compounded products contaminated with microorganisms caused at least 11 outbreaks between 2000 and 2012 (excluding the 2012 meningitis outbreak). These other outbreaks resulted in 207 infections and 17 deaths due to causes such as meningitis, septic arthritis, bloodstream infections, endophthalmitis, and systemic inflammatory response syndrome.[15]

Potency is another concern with compounded drugs. Several studies comparing the potency of compounded drugs with their FDA-approved counterparts found a high percentage of compounded samples had API amounts much lower or higher than stated.[16,17,52-56] Stark variations in potency were identified between multiple samples of the same compounded product.[16,17,52-56] In contrast, potency for almost all FDA-approved products fell within FDA guidelines,[17,52,54-56] which was consistent with an FDA statement that less than 2% of FDA-approved drugs fail routine potency testing.[16]

In 2001, the FDA evaluated 29 sterile and nonsterile compounded products from 12 pharmacies.[16] Although no drug failed purity testing, 31% (nine of 29) were subpotent, containing 59% to 89% of the reported API.[16] In 2006, the FDA conducted a similar study of 125 APIs and 36 mostly nonsterile compounded drugs, showing 33% (12/36) were subpotent or superpotent, including nine (30%) of 31 CBHT products.[17] The noncompliant products contained 68% to 268% of the expected API.[17] Some CBHT capsules that contained multiple estrogens were simultaneously subpotent and superpotent within the same finished product sample. Figure 2 illustrates an example of a finished product in which capsules contained estriol, estradiol, and estrone, wherein the concentrations of each of these estrogens varied from subpotent to superpotent among the capsules (Fig. 2).[17]

Each year, the Missouri SPB assesses a sample of drugs compounded at Missouri pharmacies. In 2013, the API for 13% of 112 products analyzed ranged from 3% to 227% of the labeled amount.[57] Of the seven drugs that failed, three were CBHTs.[57] All failed CBHT products were oral capsules: one containing estriol, estradiol, and progesterone; one with estriol, estradiol, progesterone, and dehydroepiandrosterone; and the last one delivering estriol, estradiol, and testosterone.[57]

The writer of an award-winning investigative report for *More* magazine filled 12 prescriptions for capsules containing Tri-Est and progesterone at compounding pharmacies in various states and had them analyzed at Flora Research Laboratories in Oregon.[58] Capsules differed in weight (range, 80-102 mg) and potency relative to the labeled doses of estriol (range, 67.5%-89.5%), estrone (range, 58.4%-272.5%), and estradiol (range, 95.9%-259%).[58] Most capsules contained ~80% of progesterone prescribed, and none met FDA potency requirements.[58] Although these data do not carry the weight of a formal scientific study, they raise concern as to whether women taking CBHT are receiving the doses prescribed.[58]

Compounding errors resulting in superpotent doses may increase the risk of overdose or intensify adverse effects,[59] whereas subpotent doses may not contain sufficient API to treat the condition for which they were prescribed.[17] Combined CBHT products that contain more estrogen and/or less progesterone than prescribed could fail to provide the right ratio of hormones to protect the endometrium. Increased amounts of estrogen or progesterone could also increase venous thromboembolism risk or breast stimulation.

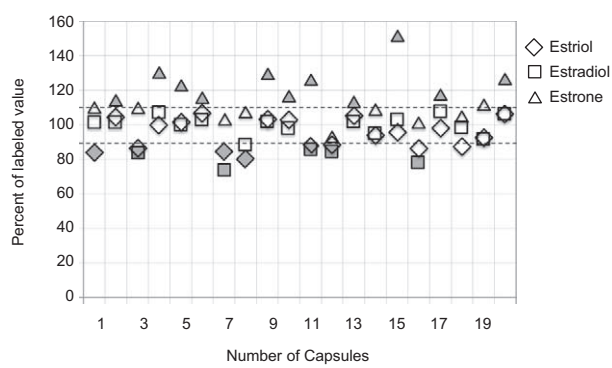

FIG. 2. Analysis of the content of individual capsules for the potency of three estrogens within a single sample of a compounded drug.[17] The *x* axis shows categories of number of capsules with each ingredient amount. Dashed lines represent 10% variation from the amount of drug declared on the product labeling. Shaded symbols fall outside of the 10% variation line.

Additional concerns regarding CBHT

Various CBHT formulations containing estrogens, progesterone, or testosterone are marketed to women with menopausal symptoms in nonsterile (eg, lotions, creams, capsules, lozenges, transdermal patches, nasal or oral products, and suppositories) and sterile (eg, injections and subdermal pellets) preparations.[7,32,60] Some CBHT medications fall into product categories the FDA considers "not appropriate for compounding under any circumstances," including extended-release, transdermal, and liposomal drugs.[2]

The FDA has never approved testosterone for postmenopausal women, and its use in CBHT regimens is controversial.[41,61] Estriol is found in many CBHT products, including Bi-Est (20% estradiol and 80% estriol) and Tri-Est (10% estradiol, 10% estrone, and 80% estriol). Although an estriol vaginal suppository is approved to treat vaginal atrophy in some countries,[61] estriol is not in any FDA-approved drug for human use, and the FDA has warned compounders not to use estriol without filing an NDA.[41,50,62,63] However, a USP monograph exists for estriol, and §503A permits compounders to use active ingredients that have a USP monograph.[30,31]

Randomized controlled trials have proven that progesterone inhibits estrogenic stimulation of the endometrium.[64,65] Administering progesterone orally or transdermally at a high enough dose to ensure sufficient bioavailability is challenging.[66,67] Many CBHT regimens incorporate nonoral progesterone, yet no adequate RCTs have established any delivery method of progesterone besides oral as effective or capable of protecting the endometrium from estrogen's effects.[7,32,60,68]

Underdosing of progesterone in an EPT regimen may increase the risk of endometrial cancer.[32,64] Cases have been published of postmenopausal women who developed irregular vaginal bleeding and were later found to have endometrial cancer after taking CBHT containing estrogen and progesterone for several years.[64,69]

The peer-reviewed literature contains no reports of adequate phase 3 trials that have proven CBHT is safe and effective, and none of the published studies on CBHT satisfy FDA guidance for clinical trials to demonstrate the safety and efficacy of a drug. Most included small sample sizes, were poorly designed, or compared unequal doses; few evaluated endometrial safety after 1 year of use.[70-76]

Authors of a systematic literature search for RCTs evaluating compounded progesterone cream for vasomotor symptoms found three RCTs, none of which applied the FDA methodology for assessing endometrial safety.[76] A few observational studies and surveys offered low-level evidence that CBHT improved menopausal symptoms, but most consolidated results for all CBHT used, ignoring differences in hormones, doses, and delivery methods.[60,73-75,77]

GUIDELINES FOR CBHT

The Endocrine Society, The North American Menopause Society, American Congress of Obstetricians and Gynecologists, American Society for Reproductive Medicine, and International Menopause Society recommend against CBHT use by anyone without a medical condition preventing them from using FDA-approved HT.[32,62,70,78-80] The FDA has also issued caution against compounded drug use.[41] Concerns include inadequate evidence of efficacy and safety, variable purity and potency, and insufficient labeling.[32,62,70,78-80] The FDA made a statement about CBHT (2008): "FDA is concerned that the claims for safety, effectiveness, and superiority that these pharmacy operations are making mislead patients, as well as doctors and other healthcare professionals. Compounded drugs are not reviewed by the FDA for safety and effectiveness. Patients who use compounded hormone drugs should discuss menopausal HT options with their healthcare provider to determine whether compounded drugs are the best option for their specific medical needs."[13]

Some CBHT prescribers use salivary or serum testing of hormone levels for titration,[81,82] but these tests are considered meaningless without pharmacokinetic data,[32] and no RCT has correlated hormone levels in saliva or serum with outcomes. An FDA statement on saliva testing to titrate CBHT says, "Hormone levels in saliva do not accurately reflect the amount of hormones a woman has in her body for the purpose of adjusting hormone therapy dose levels. A woman's hormone levels change throughout the day and from day to day."[82] None of the major menopause societies recommend using salivary testing to guide treatment[81,82]; their treatment guidelines advise to prescribe the lowest effective dose of FDA-approved HT for menopausal symptom relief.[32,62,83,84]

CONCLUSIONS

To gain approval, makers of FDA-approved products must conduct extensive testing to prove a drug is effective and safe for human use and follow strict standards for manufacturing. For HT intended-to-treat menopausal symptoms, the FDA provides specific guidance for clinical trial evaluation. Thus, FDA-approved therapies have documented safety and efficacy unlike CBHT products, which have not been rigorously tested. The FDA recommends using an approved drug over a compounded one when possible, due to their concerns about safety, efficacy and misbranding, but recognizes that some patients may need a compounded drug when no FDA-approved drug is available to meet their needs.[13] The CQA adds §503B and makes clear that §503A now applies throughout the country, removing previous obstacles and impediments to both SPB and FDA enforcement. The new law may improve compliance, accreditation, and monitoring by the compounding industry, support oversight by states and the FDA, and prevent the distribution of misbranded, adulterated, or inconsistently compounded medications, thus reducing the risk to public health.

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