

**ACCP WHITE PAPER**

# Rational and irrational use of nonsterile compounded medications

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Nonsterile compounding is a fundamental component of pharmacy practice, and compounded medications are sometimes essential to optimize a patient's medication therapy. However, controversies surround the rational use of nonsterile compounded medications. Factors including drug cost and availability and the need for a precise dosage or unique formulation may provide a legitimate reason to prepare a compounded medication. Nonetheless, clinical pharmacists should ensure a rational basis for the use of such preparations. The relative paucity of data surrounding the regulation of these formulations, as well as that surrounding their promotion and production, complicates the evaluation of their safety and efficacy. This is especially true when compounded medications are used in special cases that already lack data for the use of commercially available products. Ethical issues also surround the rational use of these nonsterile compounded medications, including the absence of their proven safety and efficacy, the lack of regulation of promotional practices regarding their use, the pricing associated with them, the strategies needed to obtain third-party coverage for them, and the limited standards in place for the actual production of compounded medications. Indeed, more evidence documenting the safety and efficacy of compounded medications is needed, together with standardization of formulations and better regulation of promotional practices and qualifications of compounding personnel. ACCP supports increased regulation of compounding to promote the appropriate use of these preparations.

**KEYWORDS**

clinical pharmacy, compounded medications, nonsterile compounding

## 1 | INTRODUCTION

Compounding is an integral component of pharmacy practice<sup>1</sup> and is often essential to meet patients' specific needs. The US Food and

Drug Administration (FDA) defines compounding as the process by which a qualified individual "combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient."<sup>2</sup> Compounding must be distinguished from manufacturing, which implies the large-scale production of medications. Manufacturing is carefully overseen by the FDA and guided by the Good Manufacturing Practices delineated in the Code of Federal Regulations.<sup>3</sup> By contrast, the primary driver for compounding is the preparation of one drug for one patient (Table 1), which makes the usual drug approval process unrealistic. However, in recent years, the demand for nonsterile compounded medications and the need to produce batches for distribution to several different patients have dramatically

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**TABLE 1** Definitions of compounding

General definition	Specific definition
<ul style="list-style-type: none"> <li>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 according to the practitioner/patient/pharmacist/compounder relationship in the course of professional practice</li> <li>Mixing of substances to prepare a drug product</li> </ul>	Includes: <ul style="list-style-type: none"> <li>Drug dosage forms prepared for both humans and animals</li> <li>Drugs or devices prepared in anticipation of prescription drug orders on the basis of routine, regularly observed prescribing patterns</li> <li>Commercial products that are reconstituted or manipulated while requiring the addition of one or more ingredients</li> <li>Drugs or devices prepared for, or as an incident-to, clinical or academic research, teaching, or chemical analysis</li> <li>Drugs and devices prepared for a prescriber's office use where permitted by federal and state law</li> </ul>

Information from: US Food and Drug Administration (FDA). Compounding and the FDA: Questions and answers. Updated October 6, 2015. Available from: [www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339764.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339764.htm). Accessed March 18, 2019; Allen L. Chapter 1. Laws, regulations, standards, and guidelines for compounding practices. In: The art, science, and technology of pharmaceutical compounding, 5th ed. Washington, DC: American Pharmaceutical Association, 2002.

increased, despite the growing number of FDA-approved medications. This has led to concern about the bioequivalence and stability of compounded medications.<sup>4,5</sup> This paper addresses the rational and irrational use of nonsterile compounded medications, the medication safety issues associated with them, and the ethical concerns that accompany the promotion, cost/billing, and production practices used by compounding pharmacies.

## 2 | RATIONAL AND IRRATIONAL USE OF COMPOUNDED MEDICATIONS

Rational drug use was defined by the World Health Organization in 1985 (Box 1).<sup>6</sup> Irrational drug use would be the use of any drug not meeting the criteria in Box 1. Compounded medications have differing and often less stringent oversight than manufactured medications, creating opportunities for irrational use. However, compounded drugs may be necessary to accomplish key elements of rational use, such as cost and availability.

Factors including drug cost and availability, dosage and formulation, and excipient allergies and intolerances may result in a rational decision to pursue compounding in specific situations. Still, clinicians should remain vigilant in reevaluating the need for compounded medications and how these preparations affect patient safety. In a recent analysis of compounding claims data, researchers showed that urgent

conditions (e.g., acute pain syndromes) often prompt the initial prescribing of compounded preparations.<sup>7</sup> These data underscore the importance of reevaluating the continued use of compounded drugs after acute needs have been met.

### 2.1 | Special populations and allergies

All populations are at risk of irrational prescribing of these products, but pediatric, geriatric, veterinary, and pregnant patients may be more likely to receive compounded therapies because of a lack of evidence supporting the use of commercially available products in these populations, as well as common drug intolerances, incompatibility with FDA-approved formulations, and a potential lack of adequate patient advocacy in veterinary and geriatric patients. In pediatric populations, compounded medications may be needed because of the lack of appropriate commercially produced pediatric formulations as well as poor palatability (e.g., undesirable taste and smell).<sup>8,9</sup> Commercially available products can have severe consequences if used inappropriately.<sup>8</sup> Similarly, geriatric patients may have difficulty safely swallowing oral medications.

The expectation that manufacturers providing FDA-approved medication will accommodate all individual patient needs is unrealistic. Clinical pharmacists can improve patient satisfaction and medication adherence, often avoiding the need for compounded therapies, by selecting and recommending optimal therapy. In some cases, use of product enhancers (e.g., lubricants or tablet crushers for oral tablets) may also be appropriate. In addition, clinicians must be made aware that excipients of compounded medications may confer risks to special populations, particularly neonates.<sup>10</sup> Clinical pharmacists who commonly encounter special populations (e.g., geriatric and pediatric patients) should be knowledgeable of the therapies and practices that may result in improved patient satisfaction and adherence. When compounded medications are necessary, clinical pharmacists can promote standardization and quality control.<sup>11,12</sup>

Hypersensitivity to drugs and drug excipients often prompts the use of compounded medications. The science of predicting and confirming true allergic responses to active and inactive ingredients is still evolving. For some drug therapies, genetic screening is becoming part of the standard of care (e.g., the *HLA-B\*57:01* allele with abacavir), but this does not extend to excipients. Patients with excipient allergies have typically identified those intolerances and allergies from prior

#### BOX 1

##### CRITERIA FOR RATIONAL DRUG USE

- Effective
- Acceptable quality
- Acceptable safety
- Accurate prescribing—drug, dose, interval, duration
- Appropriate and timely administration
- Affordable
- Dispensed correctly

Information from: World Health Organization (WHO). Conference of Experts on the Rational Use of Drugs (1985: Nairobi, Kenya). The rational use of drugs: issues suggested for consideration. Action Programme on Essential Drugs and Vaccines. Geneva: WHO, 1985.

reactions to specific triggers (e.g., lactose, dyes). Use of compounded drugs that avoid particular excipients provides a treatment option for patients with allergies to those excipients. However, the use of alternative commercial formulations and therapeutic drug interchange may also be viable solutions. Fortunately, excipient toxicity has been declining as more ingredients are chosen for their passive pharmacotoxicity profiles.<sup>13</sup> Clinical pharmacists are well positioned to evaluate these treatment challenges and identify alternatives at the point of prescribing.

## 2.2 | Compounded drugs without evidence of benefit

Compounded drugs can present opportunities for unscrupulous businesses to take advantage of populations that have disease states with relatively few reliable treatment options, such as neuropathic pain. The current market is flooded with advertisements, sometimes directly to patients, for various topical analgesics. These promotional strategies often rely on unsubstantiated testimonials. This applies to over-the-counter therapies as well as to drugs requiring a valid prescription. A survey of clinician-members of the American Society of Regional Anesthesia and Pain Medicine found that around one-fourth of clinicians reported prescribing topical compounded agents (27%) containing an average of 2.6 different ingredients (range 1-6) from a list of over 30 topical analgesics.<sup>14</sup> Most compounds contained non-steroidal anti-inflammatory drugs (NSAIDs), which have demonstrated safety and efficacy as FDA-approved formulations. However, other drugs (e.g., haloperidol, dextromethorphan, and carbamazepine) often included in combination with NSAIDs have no or few (often small and uncontrolled) studies in humans showing evidence for use as a topical analgesic, thus representing irrational use. Despite the lack of robust evidence, proponents describe these compounded medications as “rational topical polypharmacy,” postulating that different drugs targeting different pain pathways create synergy.<sup>15</sup> This practice adds a new layer of concern for health care providers by creating scenarios in which one or more components of a product are rational while others are not.

Another important example of irrational use of compounded drugs involves compounded bioidentical hormone replacement therapy (BHRT) as an alternative therapy for patients concerned with the safety of manufactured hormone replacement therapy. One regimen, called the Wiley Protocol, claims that its creams are prepared with “FDA-approved pharmaceutical grade ingredients,” prescribed by Wiley-trained providers, and dispensed by Wiley Registered compounding pharmacies, making the Wiley Protocol BHRT superior to other compounded BHRTs.<sup>16</sup> However, published data from the Wiley Protocol are lacking to substantiate this claim. In addition, a bio-ethicist evaluation of the Wiley Protocol advertisements found several ethical concerns: the protocol could be classified as human research but did not meet current research standards because it failed to use standard research ethics guidelines (e.g., informed consent, scientific methodology, and investigator expertise) and involved questionable methods of participant enrollment and sources of funding.<sup>17</sup> Evidence does not support a clinical advantage of BHRT over conventional hormone replacement therapies, nor has the safety and efficacy of BHRT

been established.<sup>18,19</sup> Common issues with each of these examples (polypharmacy in compounded topical analgesics and the Wiley Protocol) center on the fact that participants are vulnerable and poorly informed of the risks that come with investigational therapy as well as the fact that appropriate regulation and oversight are lacking. Clinical pharmacists should recommend evidence-based alternatives when questionable compounded medications are being considered.

### 2.2.1 | Impact on medication safety

In addition to lack of efficacy, safety is a concern when using medications topically. The term *safety* not only encompasses both sterility and stability, but also the appropriateness of creating formulations when safety data are limited. For example, the use of clonidine in compounded analgesics has produced significant safety concerns.<sup>20,21</sup> Clinical pharmacists caring for special populations, including pediatric and geriatric patients, must evaluate the risk-benefit of compounding enteral formulations of medications that cannot be taken as manufactured. In pediatric patients, the use of compounded medications often involves an overall lack of drug safety and efficacy data. Off-label pediatric use of certain manufactured medications such as pemo-line and cisapride has resulted in severe adverse events that led to market withdrawal of these drugs.<sup>22,23</sup> The FDAMA, the Best Pharmaceuticals for Children Act, and the Pediatric Research Equity Act have prompted manufacturers to conduct more studies in pediatric patients. However, data on the use of most medications in pediatric patients remain sparse.

For decades, pharmacists have struggled with the paucity of compounding recipes, especially those containing reliable stability and sterility information. These recipes are often based on single published case reports or case series, unpublished institution-specific formulas, or even “word-of-mouth” references. Issues of compounding safety are aptly illustrated by the example of compounded lansoprazole suspensions. The first published enteral lansoprazole suspension recipe, which appeared in the July 1999 issue of the *American Journal of Gastroenterology*, involved the combination of powder from lansoprazole capsules and sodium bicarbonate parenteral solution.<sup>24</sup> Since its initial publication, multiple researchers have examined the stability of this combination, with conflicting results. The beyond-use date in these articles ranges anywhere from 14 to 90 days if refrigerated, or from 8 hours to 90 days at room temperature.<sup>24-26</sup> Additional recipes were created to make the suspension more palatable. One recipe published in 2014 adds a flavored suspending agent to the original compound, with the authors providing a beyond-use date of 90 days either refrigerated or stored at room temperature.<sup>27</sup>

With greater access to technology, many researchers have begun analyzing these older recipes, using the same stability standards as the FDA requires of manufacturers. One study using liquid chromatography-tandem mass spectrometry to evaluate the stability of the 1999 lansoprazole suspension determined that the suspension's refrigerated shelf life was much shorter than previously reported.<sup>28</sup> With this new finding, the expiration date for the 1999 compounded product was modified from 14 to 7 days under refrigeration. The example of inconsistencies with recipes for lansoprazole oral

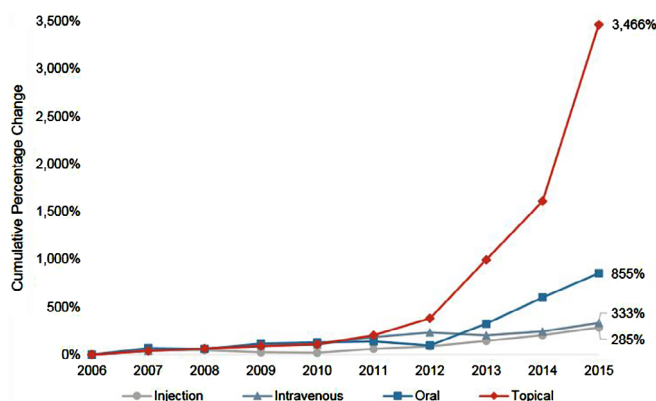
## BOX 2

## SAFETY ISSUES ASSOCIATED WITH NONSTERILE COMPOUNDING

- (1) Multiple compounding recipes exist for the same medication
- (2) Multiple concentrations of the same compounded medication exist, and bioequivalence data are scarce
- (3) Published recipes are not overseen by any regulatory body
- (4) There are no standards for testing the safety, stability, efficacy, or effectiveness in the specific populations for which they were designed
- (5) Stability information is not obtained in a manner consistent with the FDA guidelines for bioanalytical testing used by medication manufacturers
- (6) No standardized methodology for testing the stability or sterility of the recipe
- (7) Minimal details are provided for adequate storage of compounded medication
- (8) Minimal/no safety data in humans

suspension underscores the many safety issues currently associated with extemporaneous compounding (Box 2).

For patients who require treatment with narrow therapeutic index (NTI) drugs, compounds that lack the anticipated potency and stability are potentially harmful. In a review of extemporaneously prepared products for oncologic indications, only 14 of the 21 oral liquid formulations (67%) with published recipes had data on chemical stability, and only three (14%) had additional physical stability data.<sup>5</sup> Furthermore, bioavailability data for these compounded products were similarly scarce and only available for seven (33%) of the oral solutions prepared from solid dosage forms. A lack of sufficient investment in clinical trials, limited research on drug disposition, unapproved uses of



**FIGURE 1** Growth in Part D spending for compounded drugs by form, 2006 to 2015. Information from: US Department of Health & Human Services, Office of Inspector General (HHS OIG). High Part D spending on opioids and substantial growth in compounded drugs raise concerns. HHS OIG data brief. June 2016. OEI-02-16-00290. Available from <https://oig.hhs.gov/oei/reports/oei-02-16-00290.pdf>. Accessed March 18, 2019

**TABLE 2** Managed care strategies to mitigate the cost of compounded drugs

Prior authorization criteria	Other strategies
Exclusion of: <ul style="list-style-type: none"> <li>• Non-FDA-approved bulk powders</li> <li>• Over-the-counter products</li> <li>• Cosmetic products</li> <li>• Cosmetics not FDA approved for the route of administration</li> <li>• Ingredients not FDA approved for the intended use</li> </ul> Trial of an FDA-approved commercially available drug first Requirement for clinical studies to support use	Ingredient-based claims processing logic Quantity limits on crushed tablets Checking claims for duplicate ingredients Exclusion of high-cost compounds from member benefit

therapies in special populations (eg, pediatric), extensive safe handling requirements, complexity of bioavailability studies, and legal red tape are potential reasons why these data are not available. Therefore, use of national guidelines to promote standards of practice for dispensing and compounding therapies with NTI drugs (eg, oral chemotherapy) represents one viable solution.

Currently, national efforts are under way to standardize concentrations of nonsterile oral compounds. For example, the American Society of Health-System Pharmacists (ASHP) Standardize 4 Safety (S4S) initiative is charged with developing and implementing standard oral compounded liquid medication concentrations.<sup>29</sup> Criteria for inclusion on S4S's list of approved oral compounded liquid medication recipes include peer-reviewed, published recipes; stability longer than 7 days; uncomplicated compounding procedures and dose measurements; and overview by an interprofessional panel of experts. This effort highlights one approach toward safer oral compounded liquid medications and serves as a valuable resource for clinical pharmacists.

## BOX 3

## USP (795) TRAINING RECOMMENDATIONS FOR NONSTERILE COMPOUNDED PRODUCTS

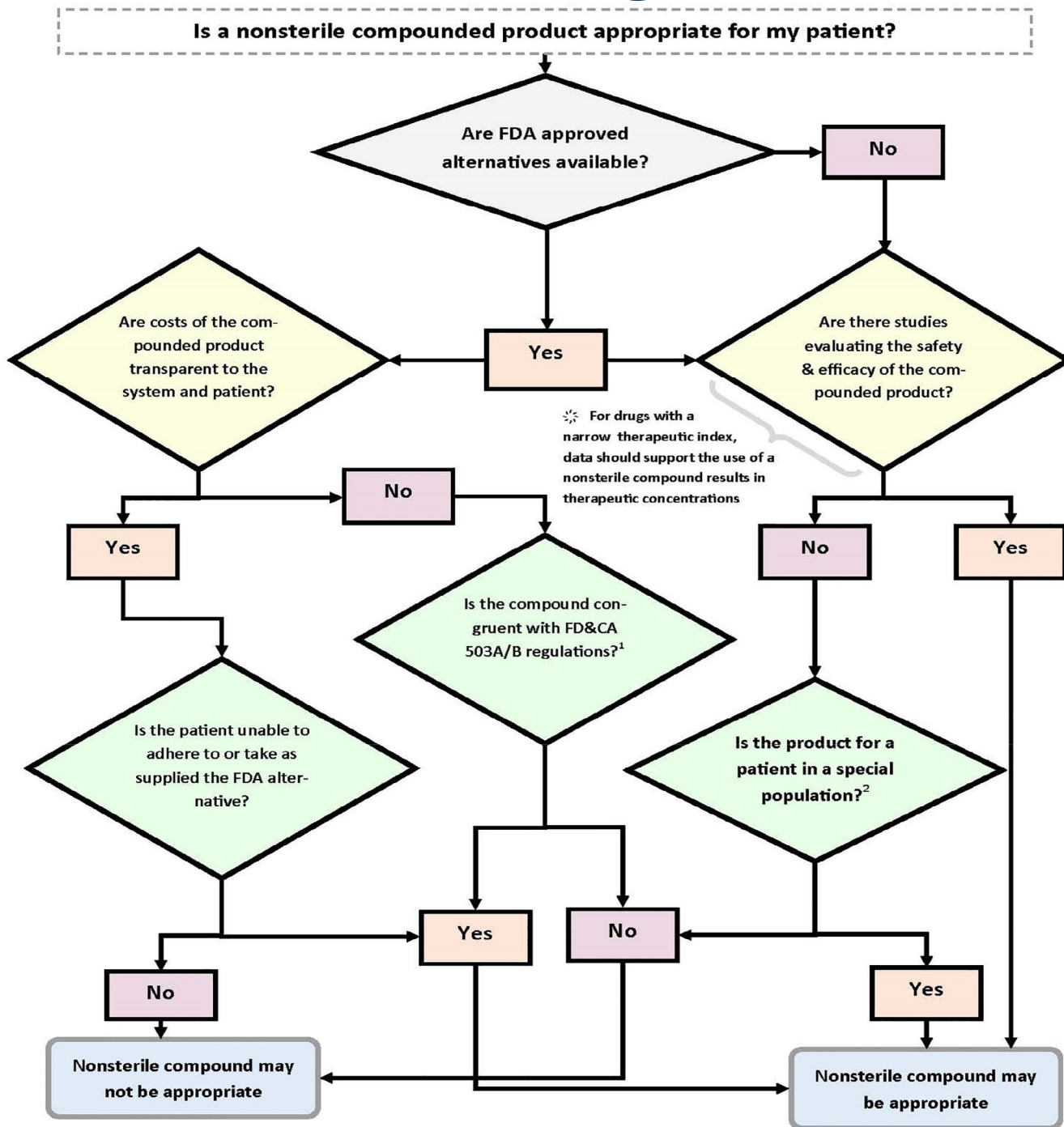
1. All employees involved with pharmaceutical compounding should read and become familiar with the USP Pharmacists' Pharmacopeia and other relevant publications, including how to read and interpret material safety data sheets (MSDSs)

2. All employees shall read and become familiar with each of the procedures related to compounding, including those involving the facility, equipment, personnel, actual compounding, evaluation, packaging, storage, and dispensing

3. All personnel who compound using hazardous drugs shall be fully trained in the storage, handling, and disposal of hazardous drugs (before the handling of hazardous drugs)

*\*USP (795) training requirements have been truncated to include only items relevant to qualifications for preparing nonsterile compounds.*

Information from: United States Pharmacopeia (USP) chapter <795> standards. Pharmaceutical compounding—nonsterile preparations. Available from [www.usp.org/usp-nf/official-text/revision-bulletins/pharmaceutical-compounding-nonsterile-preparations](http://www.usp.org/usp-nf/official-text/revision-bulletins/pharmaceutical-compounding-nonsterile-preparations). Accessed March 19, 2019.



**FIGURE 2** Decision tree for the use of nonsterile compounded products

<sup>1</sup>Refers to section 503A/B of the Federal Food, Drug, and Cosmetic Act.<sup>34,35</sup>

<sup>2</sup>Special populations include, but are not limited to, pediatric, geriatric, veterinary, and pregnant patients

### 3 | PROMOTION OF NONSTERILE COMPOUNDING

Promotion of compounding has proved to be an area of significant controversy because compounded medications are not subject to the same regulations as manufactured drugs. Marketing and promotion of manufactured pharmaceutical products has been regulated by the FDA since the Federal Food, Drug, and Cosmetic Act (FD&C) was implemented in 1938. Efforts to regulate compounding materialized much later. The FDA developed the Compliance Policy Guide (CPG) in

1992 to provide insight on the delineation of compounding and unlicensed manufacturing.<sup>30</sup> The CPG enabled the FDA to discipline a pharmacy when the pharmacy's activities resembled manufacturing. In 1997, the FDA passed the Food and Drug Administration Act (FDAMA; 21 USC §353a), which protected compounded pharmaceuticals from being classified as new drugs "only if the pharmacy, licensed pharmacist, or licensed physician does not advertise or promote the compounding of any particular drug, class of drug, or type of drug" (21 USC 353a(c)).<sup>30</sup> The US court system ruled that the restriction on



advertising and promotion was unconstitutional and not enforceable by the FDA. Therefore, §353a(c) was removed from the statute.

Because of the lack of regulation, prescribers, compounding pharmacies, and marketing agencies have at times engaged in unethical promotional practices. In a notable example, physicians were solicited to prescribe compounded pain medications consisting of maximally reimbursed ingredients, often without an existing physician-patient relationship. After payment was remitted to the pharmacy, individuals involved in marketing these compounded medications and the prescribing physicians received monetary compensation.<sup>31</sup> Although these cases do not represent most nonsterile compounding practices, they do suggest the need for closer oversight and stricter regulations on compounding promotion.

## 4 | COST

For compounded drugs, both the rising costs of FDA-approved therapies and the costs of the compounded preparations themselves are important considerations for clinical pharmacists.

### 4.1 | Price gouging and drug shortages

The publicity surrounding recent price-gouging scandals has highlighted the widespread impact of this practice on the nation's current health care system. Some critics have suggested that federal agencies such as the FDA should play a more active role in ensuring patient access to affordable therapy.<sup>32</sup> Although the FDA does not set drug prices,<sup>33</sup> it does affect competition within the market through its approval of generic competitors. The process of generic drug approval can be lengthy and expensive, dissuading companies from entering a niche drug market with limited sales potential. However, with thousands of yet-to-be-reviewed generic drug applications, the FDA could play a more active role by temporarily permitting the compounding of drugs subject to abrupt shortages or price gouging. Large-scale solutions have begun in the commercial sector, with Express Scripts, Inc. (ESI) promoting its \$1 per capsule compounded alternative to Turing Pharmaceuticals' \$750 per tablet Daraprim (pyrimethamine).<sup>34</sup> ESI's past criticism of the compounding industry's price-gouging attempts did not deter it from turning to compounding to combat price gouging from pharmaceutical manufacturers.<sup>35</sup>

Arguably, the most informative example of the regulatory controversy to date is illustrated by the FDA decision not to enforce the proliferation of unapproved compounded formulations of Makena (hydroxyprogesterone caproate).<sup>36</sup> After a dramatic price increase for Makena in 2011, compounding pharmacies were prompted to compound cheaper products with the active ingredient in Makena, hydroxyprogesterone caproate. However, KV Pharmaceutical Company (KV), the maker of Makena, presented evidence to the FDA that questioned the purity and potency of the compounded alternatives. In its review, the FDA reinforced its stance that approved drugs (e.g., Makena) provide a greater assurance of safety and effectiveness than compounded drugs but, after analysis of the limited number of compounded samples, did not identify any major safety problems associated with the compounded products. KV responded by filing a four-

count complaint in federal court demanding declaratory and injunctive relief because of the FDA's "unwillingness" to enforce, but the case was dismissed by a US District Court, allowing the continued availability of compounded hydroxyprogesterone caproate.<sup>37</sup>

Recently, the Center for Drug Evaluation and Research (CDER) released nonbinding industry guidance for compounded drug products that are "essentially copies of approved drugs" within both 503B<sup>34</sup> and 503A<sup>35</sup> compounding pharmacy settings. Specific language defines "essentially copies of approved drugs" within the FD&C Act,<sup>3</sup> and CDER's additional recommendations provide helpful insight into the FDA's current thinking. The CDER guidance for 503A compounding pharmacies states that a compound is "essentially a copy of a commercially available product" when it has the same active pharmaceutical ingredient at the same (or similar) dosage and route of administration. Drugs are not considered "commercially available" (and are therefore not applicable to the guidance) when they have been discontinued, are no longer marketed, or appear on the FDA drug shortage list as "currently in shortage" (pursuant to section 506E of the FD&C Act). Because shortage status varies, the CDER guidance document recommends a specific notation of shortage status on compounded prescriptions (i.e., date the drug was on the shortage list and the last time the list was checked).

Given the recent price-gouging attempts by pharmaceutical manufacturers and drug shortages, use of compounded alternatives to FDA-approved therapies can seem appealing and rational. However, the Principles of Compounding of the Pharmacy Compounding Accreditation Board do not consider the differences in price between FDA-approved drugs and compounded drugs "significant" enough to justify compounding on its own.<sup>36</sup> In addition, compounding copies of commercially available products, regardless of cost, creates conflict between facilities compounding under 503A and 503B exemptions and current CDER guidance.<sup>34,35</sup> Fortunately, there are alternatives to consider when drug price or supply affects the efficiency of care. Pharmacists are at the front lines of these drug shortage and price-gouging cases that undermine patient access and must assist with efforts to promote safety and efficiency. Regardless of practice setting, pharmacists should stay current in their knowledge of drug shortages,<sup>37</sup> generic and therapeutic drug interchanges,<sup>38</sup> and use of drug alternatives with similar outcomes to facilitate optimal patient care.

### 4.2 | Costs of compounded drugs

Costs and use of compounded drugs have rapidly increased for both public and private insurers over the past decade. In 2016, the Health & Human Services Office of Inspector General (HHS OIG) reported a 625% increase (from \$70.2 to \$508.7 million) in Part D spending on compounded drugs during 2006-2015 (see Figure 1).<sup>4</sup> Topical and oral compounded drug spending (3466% and 855% spending growth, respectively) clearly outpaced injection and intravenous spending (285% and 333% spending growth, respectively) over the same 9-year period. The HHS OIG report outlined cases of fraud and abuse amid this growth. Accordingly, Medicare updated its *Prescription Drug Benefit Manual* to limit coverage of compounded drugs to only those that contain at least one ingredient that independently meets the definition of a Part D drug, and that only the cost of those components are allowable costs under Part D.<sup>39</sup>

The trend of increased Medicare Part D spending on compounded drugs occurred quickly, with the greatest spending jumps in 2012-2015. Growth in the number of prescriptions as well as the spending for compounded prescriptions also increased for private insurers. In a sample of over 22 million commercially insured members, the prevalence of prescription compound users increased from 1.1% to 1.4% from 2012 to 2013, reflecting a 27.3% increase in using members. The total number of compounded prescriptions rose by 34.2%, totaling 653 360 in 2013. The mean compounded ingredient cost in this sample increased by 130%, from an average of \$308 in 2012 to \$710 in 2013. For comparison, in the same period, the mean ingredient cost of a noncompounded prescription increased by only 7.7%.<sup>7</sup> Another insurer reported more than a 10-fold increase in the cost of compounded prescriptions over a 2-year period, rising from an average cost of \$90 per claim to \$1100 per claim.<sup>40-42</sup>

Managed care organizations (MCOs) have responded to rising trends in use and cost by increasing regulation of compounded medications, which translates to increased costs for patients. ESI reported a jump in client spending from \$28 to \$171 million on compounded drugs between 2012 and 2014.<sup>43</sup> The regulatory efforts by MCOs are primarily meant to prevent unnecessary use, overspending, and risk associated with compounded medications. If MCOs did not take steps to control spending, the resulting effect would translate to higher premiums and deductibles for beneficiaries. Patients are already challenged with rises in premiums and deductibles because of increasing overall health care costs, and efforts to thwart further increases are necessary.

Although coverage of high-dollar compounded prescriptions by MCOs may be tightly regulated, there are mechanisms for beneficiaries with medically necessary indications to receive coverage. Utilization management, a common form of cost control, includes the implementation of prior authorization programs together with other strategies that target the use of high-dollar compounds exceeding a threshold (see Table 2).<sup>40,41</sup> Some strategies have been only marginally successful. ESI reported that some compounders adapted quickly to the bulk chemical ban by "crushing massive numbers of tablets" for incorporation into dermatologic bases.<sup>44</sup> The company further cited one egregious example of a single compound containing over 2000 crushed tablets; many pharmacy benefit managers (PBMs) now limit the covered quantity of crushed tablets. Modifications to this approach seem successful, given that ESI reported a 76.4% decline in per member per year (PMPY) spending in 2016, and OptumRx reported a 90% decline in PMPY (from 2014 to 2015) in total compound spending.<sup>41,43</sup> However, the chief pharmacy officer for OptumRx admits that issues remain, such as "price rolling" (incremental retrieval-and-error claim submissions) and "prescription splitting" (billing small increments over several days to avoid cost ceilings).<sup>41</sup>

Pharmacists are undoubtedly feeling the ripples of this tug-of-war when interacting with patients directly. Payers and PBMs have reacted swiftly by closing the door on some compounders, which may leave some patients feeling stranded. Clinical pharmacists can assist patients by exploring and validating patient concerns, recognizing safety issues, and triaging next steps. In addition, clinical pharmacists can identify cost-effective and evidence-based alternatives, or monitor the safety and efficacy of compounded drugs when they are to be

continued. For patients without prescription coverage and limited financial resources, pharmacists can assist by recommending less costly therapeutic alternatives and identifying prescription assistance programs and copayment cards for FDA-approved therapies. In some cases, a compounded medication is the most cost-effective option. However, in these situations, use of a more affordable compounded product may help improve patient adherence and satisfaction. In these cases, the balance between uncertain safety and efficacy should be reviewed before initiation. Variation in pricing exists among compounding pharmacies. The pharmacy that compounds the highest-quality product at the most economical price should be used.

## 5 | QUALIFICATIONS

Another controversy surrounding nonsterile compounding revolves around who should perform compounding functions and what education or qualifications are necessary. The FDA simply states that compounding may be done by a pharmacist, a physician, or someone under the supervision of a licensed pharmacist.<sup>2</sup> The United States Pharmacopeia (USP) General Chapter 795, however, provides recommendations for individuals responsible for compounding nonsterile preparations. To be proficient in compounding, responsible parties must be familiar with the standards and guidance related to compounding (eg, Pharmaceutical Compounding—Sterile Preparations (797)) and the applicable compounding laws. Specific training recommendations are summarized in Box 3. In addition to the USP guidance, professional organizations provide additional recommendations, though there is little consensus among them. An ASHP technical bulletin states that a compounding pharmacist should be a trained expert in the field.<sup>45</sup> ASHP also delineates selected recommended components of this training, including proper use of equipment; compounding techniques; properties of products, including stability and storage and handling requirements; and handling of hazardous substances. In addition, this bulletin notes that pharmacists are allowed to supervise personnel while compounding, but does not state what training or education these individuals should complete. The American Pharmacists Association (APhA) indicates that pharmacists within compounding specialty pharmacies often have additional training beyond pharmacy school.<sup>46</sup>

Although some federal laws govern compounding, most compounding is regulated at the state level, with each state having its own unique guidelines. Only two states, Georgia and New York, require a practical compounding examination before pharmacist licensure. In addition, neither of these states allows pharmacy technicians to compound.<sup>47</sup> States often regulate whether student pharmacists are allowed to compound. However, in most cases, student pharmacists are allowed to compound with pharmacist supervision.

## 6 | CONCLUSION

Compounding will likely remain an integral part of pharmacy practice because some patients will always need individualized therapies that are not available commercially. Clinical pharmacists working within

their respective specialties (e.g., pediatric and geriatric care) should maintain their status as drug therapy experts, including for both FDA-approved and compounded therapies. Because practitioners regularly encounter the use of dietary supplements, natural products, and other non-FDA-approved therapies, they should be trained to evaluate the safety and efficacy of compounded drugs with similar scrutiny and skepticism. Addressing ethical considerations as they relate to cost can be challenging, but restricted coverage has made obtaining these compounded drugs more difficult for the patients who truly need them. Clinical pharmacists must act as whistleblowers when patients receive compounded drugs in the absence of safety or efficacy data. Similarly, clinical pharmacists must also recognize that certain patient characteristics (eg, excipient allergies, incompatibility to available dosage formulations) or instances of price gouging and drug shortages may precipitate the need for compounded drugs in both acute and chronic settings. A flowchart to assist pharmacists in evaluating the appropriateness of compounded nonsterile products is provided in Figure 2.

More evidence supporting the safety and efficacy of compounded medications in a wide variety of populations is needed to support their use, because few data support the purity, stability, potency, and bioequivalence of nonsterile compounds. Efforts to standardize nonsterile oral compound recipes on the basis of safety, efficacy, and stability data are important, but require adequate oversight. ACCP supports increased regulation of compounding to promote the appropriate use of compounded medications.

## ENDNOTE

<sup>a</sup>See, for example, section 503B(d) (2) of the FD&C Act: "A drug that is identical or nearly identical to an approved drug, or a marketed drug not subject to section 503(b) and not subject to approval in an application submitted under section 505, unless, in the case of an approved drug, the drug appears on the drug shortage list in effect under section 506E at the time of compounding, distribution, and dispensing (section 503B(d) (2)(A)); or A drug, a component of which is a bulk drug substance that is a component of an approved drug or a marketed drug that is not subject to section 503(b) and is not subject to approval in an application submitted under section 505, unless there is a change that produces for an individual patient a clinical difference, as determined."

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